“MEAN PLATELET VOLUME AS A NOVEL MARKER FOR INCREASED CARDIOVASCULAR RISK IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE”

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CERTIFICATE

This is to certify that the dissertation entitled **" MEAN PLATELET VOLUME AS A NOVEL MARKER FOR INCREASED CARDIOVASCULAR RISK IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE"** is the bonafide work of **Dr. VINOTH S** in partial fulfilment of the university regulations of the Tamil Nadu Dr.M.G.R Medical University, Chennai, for M.D General Medicine Branch I examination to be held in April 2017.

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DECLARATION

I **Dr.VINOTH S** solemnly declare that, this dissertation "**MEAN PLATELET VOLUME AS A NOVEL MARKER FOR INCREASED CARDIOVASCULAR RISK IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE"** STUDY is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr R PRABHAKARAN** MD Professor,Department of General Medicine, Madurai Medical College, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of **M.D Degree General Medicine Branch-I;** examination to be held in **April 2017.**

Place: Madurai

Date: **Dr.VINOTH S**

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INTRODUCTION:

“Nonalcoholic fatty liver disease (NAFLD) is emerging as an important cause of liver disease in India. Epidemiological studies suggest prevalence of NAFLD in around 9% to 32% of general population in India with higher prevalence in those with overweight or obesity and those with diabetes or prediabetes”.

“Non Alcoholic Fatty Liver Disease (NAFLD) is a disease characterized by excessive deposition of fat (steatosis) within the hepatocytes . This disease comprises a wide range of pathological changes rangingfrom steatosis to Non Alcoholic Steatohepatitis(NASH) with inflammation of the liver.The most common cause of death in patients with NAFLD is cardiovascular death accounting for 48% of mortality while liver related deaths occur only in 7% of the patients”.

“Non-alcoholic fatty liver disease (NAFLD) and Non-alcoholic steatohepatitis (NASH) are associated with cardiovascular events and Metabolic Syndrome (MetS). NAFLD is considered to be a hepatic manifestation of MetS and has become an important public health issue because of its high prevalence. It is currently being considered an independent Cardiovascular disease (CVD) risk factor.”

“Obesity, type 2 diabetes mellitus and hyperlipidaemia are coexisting conditions frequently associated with NAFLD. Because of the strong association with various metabolic abnormalities, NAFLD is now considered a part of spectrum of metabolic syndrome . Patients with metabolic syndrome are at an increased risk for atherosclerosis and cardiovascular disease. In the Third National Health and Nutrition Examination Survey, metabolic syndrome was significantly related to myocardial infarction in either gender. In the Atherosclerosis Risk in Communities (ARIC) study, the subjects with metabolic syndrome were approximately 1.5–2 times more likely to develop coronary artery disease than the controls.This puts patients with NAFLD also at an increased risk for atherosclerosis and cardiovascular disease.”

“Mean Platelet Volume (MPV) is an indicator of platelet function and activation.

Platelets play a vital role in hemostasis and mean platelet volume (MPV) is a measure of average size and platelet activity. Larger platelets are more thrombogenic and contribute to atherosclerosis.The cause of increased MPV in patients with NAFLD is due to low grade inflammatory state induced by hepatic steatosis leading to platelet activation.Increase in MPV is also well documented in metabolic syndrome, stroke and diabetes mellitus .It is a simple test that can be done during routine Complete Blood Count. Hence, MPV can be used as simple and cost-effective hematological parameter for predicting cardiovascular events”.

“Thus this study is done to compare MPV values of the patients with NAFLD and of the patients without fatty liver disease and to investigate whether this increased MPV is associated with increased cardiovascular disease in patients with NAFLD “.

REVIEW OF LITERATURE

“According to Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association Non alcoholic fatty liver disease and related disease’s definition are as follows

NON ALCOHOLIC FATTY LIVER DISEASE (NAFLD) Encompasses the entire spectrum of fatty liver disease in individuals without significant alcohol consumption, ranging from fatty liver to steatohepatitis and cirrhosis.”

“Ongoing or recent alcohol consumption > 21 drinks on average per week in men and > 14 drinks on average per week in women is a reasonable definition for significant alcohol consumption when evaluating patients with suspected NAFLD in clinical practice”.

“NONALCOHOLIC FATTY LIVER (NAFL) is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury in the form of ballooning of the

hepatocytes or no evidence of fibrosis. The risk of progression to cirrhosis and liver failure is minimal".

" NONALCOHOLIC STEATOHEPATITIS (NASH) indicates the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure and rarely liver cancer."

"NASH CIRRHOSIS is the presence of cirrhosis with current or previous histological evidence of steatosis or steatohepatitis"

"Cryptogenic Cirrhosis is the presence of cirrhosis with no obvious etiology. Patients with cryptogenic cirrhosis are heavily enriched with metabolic risk factors such as obesity and metabolic syndrome".

"NAFLD Activity Score (NAS): An unweighted composite of steatosis, inflammation, and ballooning scores. It is a useful tool to measure changes in liver histology in patients with NAFLD in clinical trials".

"Therefore to define a patient having NAFLD there should be evidence of hepatic steatosis either by imaging or by histology and there should not be any cause of secondary hepatic fat accumulation such as significant alcohol consumption , use of steatogenic medications or hereditary disorders."

“ NAFLD is assuming higher importance now because of:

1. The possible role in the development of cardiovascular disease

2. The association with diabetes and impaired glucose tolerance

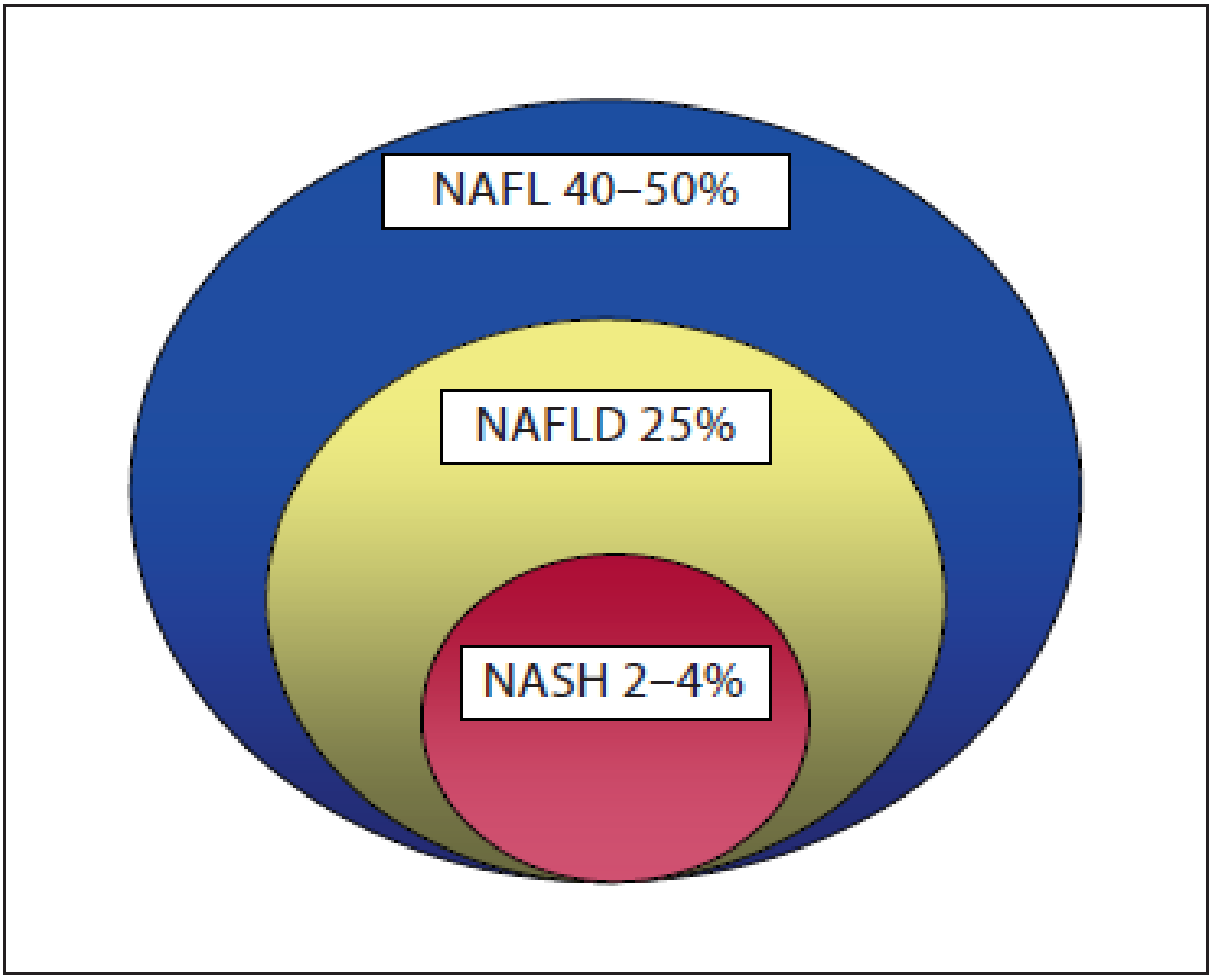
3. The strong relationship with metabolic syndrome.”

“CARBOHYDRATE DEFICIENT TRANSFERRIN (CDT) is a specific biomarker of chronic alcohol abuse. It has a half life of more than 15 days. The presence of high levels of CDT excludes the diagnosis of NAFLD.”

“EPIDEMIOLOGY OF NAFLD:

The prevalence of NAFLD is rapidly increasing worldwide in parallel with the increase in obesity and type 2 diabetes . It is important to note that this prevalence is partly dependent upon the method used to diagnose NAFLD, the method used to assess alcohol intake and the cutoff point used to exclude ‘relevant’ alcohol intake . The prevalence of NAFLD in the general population is estimated to be 20–30% in Western countries and 15% in Asian countries” .

“The prevalence of NAFLD varies according to age, gender and weight status. NAFLD and the NASH have been reported in subjects of all ages, including children, where the prevalence of steatosis is smaller than in adults (13–15%), but increases in presence of obesity (30–80%) . As a rule, the prevalence of NAFLD increases with age, with higher values in males between 40 and 65 years. The most reliable values for the prevalence of NAFLD and NASH in the general population are 20–30% and 2–3%, respectively. Owing to the increased prevalence and incidence of obesity and diabetes, in the next few” years NAFLD may represent the principal cause of liver disease worldwide and possibly the first cause of liver transplantation .



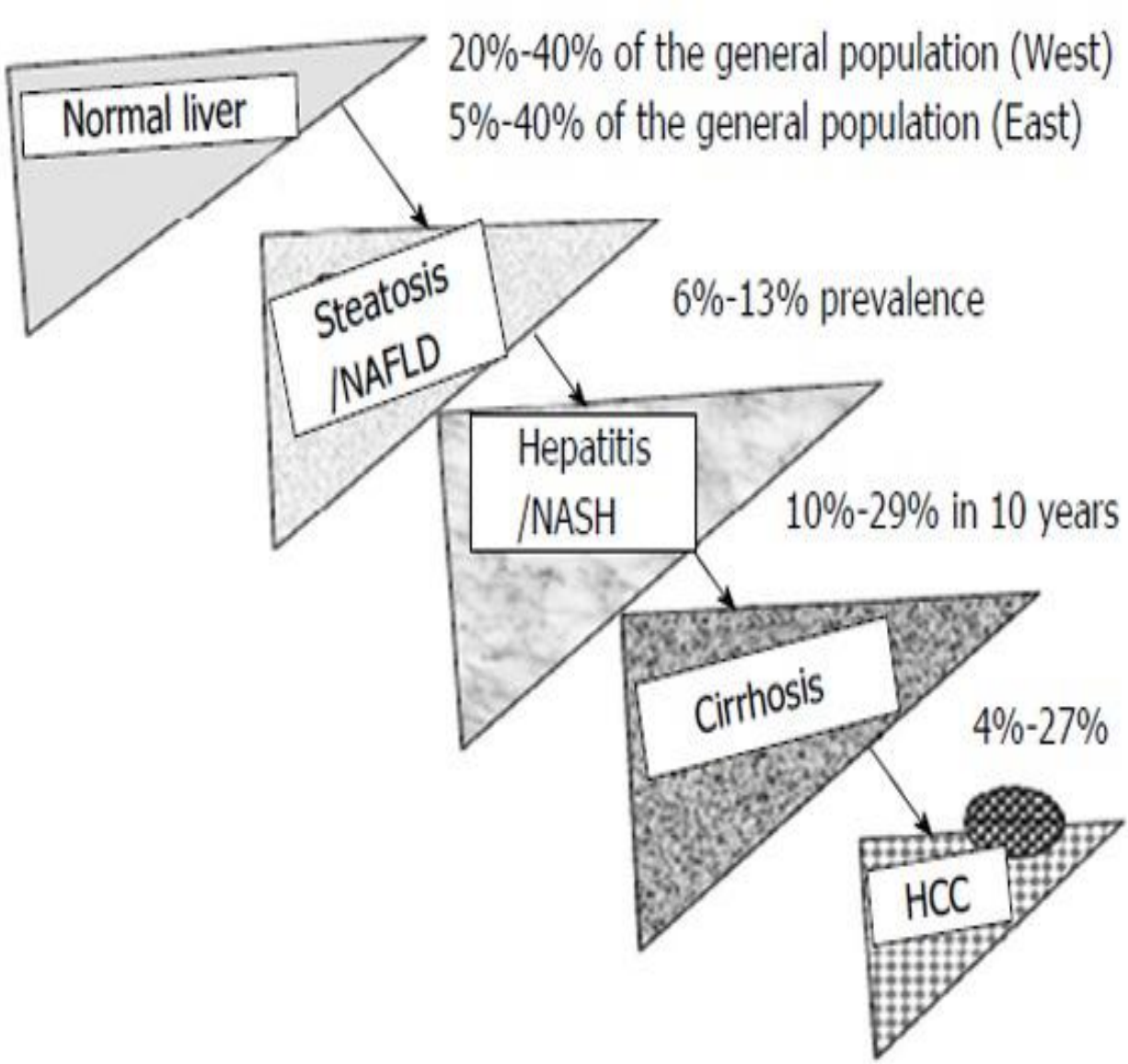
ESTIMATED PREVALANCE OF NAFL, NAFLD, NASH

INDIAN SCENARIO:

“The prevalence of NAFLD in india is around 10-32%,according to NHANES data ,the prevalence of NAFLD has been increasing over the past 3 decades accounting to nearly 50 to 75% of chronic liver disease.diabetes,central obesity,insulin resistance and dyslipidemia are common predisposing factors.India has the largest number of people with diabetes in the world.Asian Indians are more prone to have insulin resistance and have increased waist circumference and visceral fat.With increasing obesity and diabetes,there is a high possibility of thr prevalence of fatty liver increasing further”.

NATURAL HISTORY OF NAFLD

“A major focus of the NAFLD-related chronic diseases during the last 10 years has involved chronic liver disease, cardiovascular disease (CVD) and T2DM; e.g., a recent meta-analysis showed that NAFLD increased overall mortality by 57% mainly from liver related and CVD causes, and increased risk of incident T2DM by approximately twofold .There is emerging evidence that NAFLD is linked to other chronic diseases, such as sleep apnea, colorectal cancers, osteoporosis, psoriasis and various endocrinopathies (e.g., polycystic ovary syndrome), CKD”



NATURAL HISTORY OF NAFLD

RISK FACTORS ASSOCIATED WITH NAFLD

Conditions with established association:

1. Obesity

2.Type 2 diabetes mellitus

3.Dyslipidemia

4.Metabolic syndrome.

Conditions with emerging association:

1. Polycystic ovary syndrome

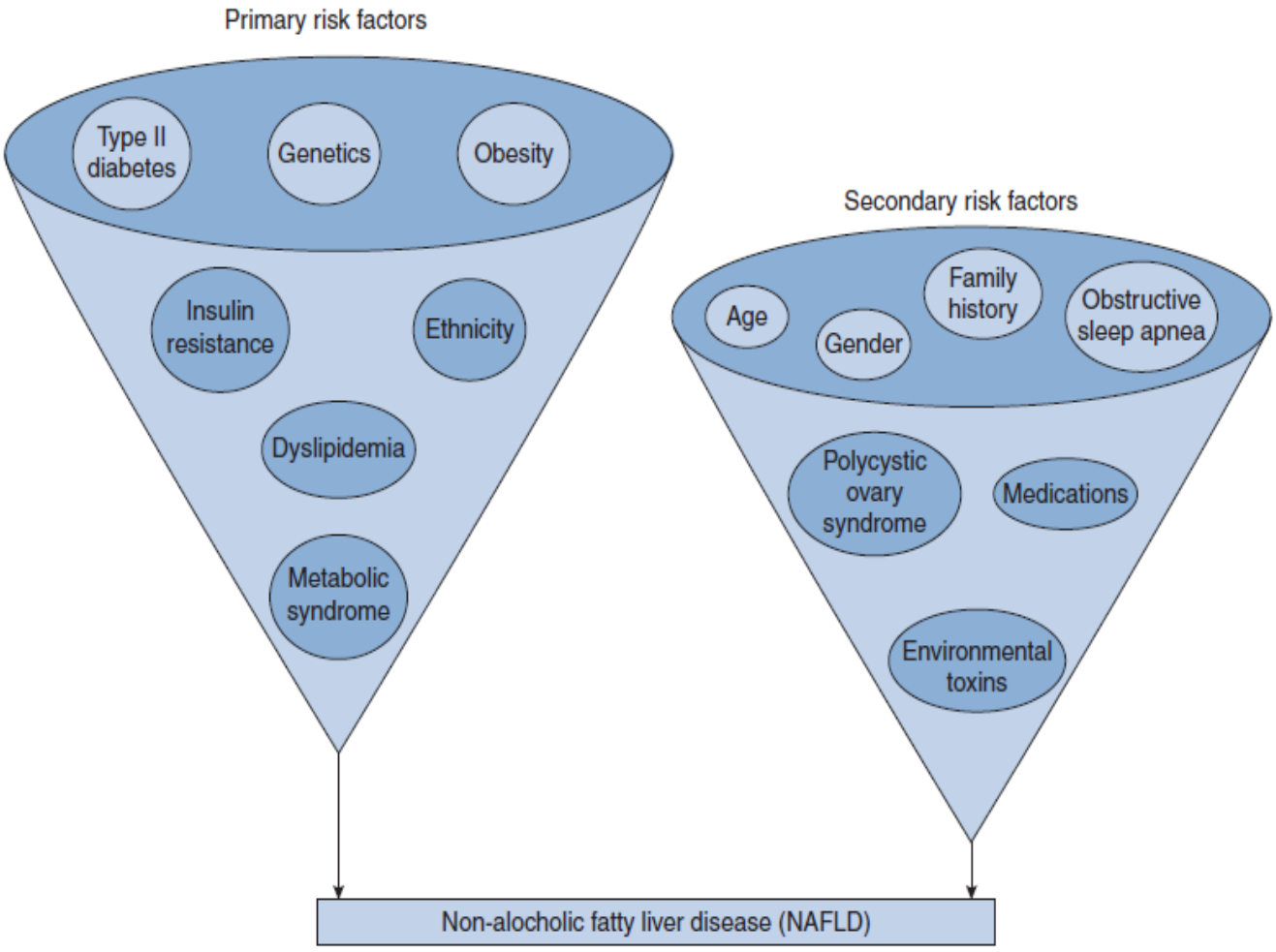
2. Hypothyroidism

3.Obstructive Sleep apnea

4.Hypopituitarism

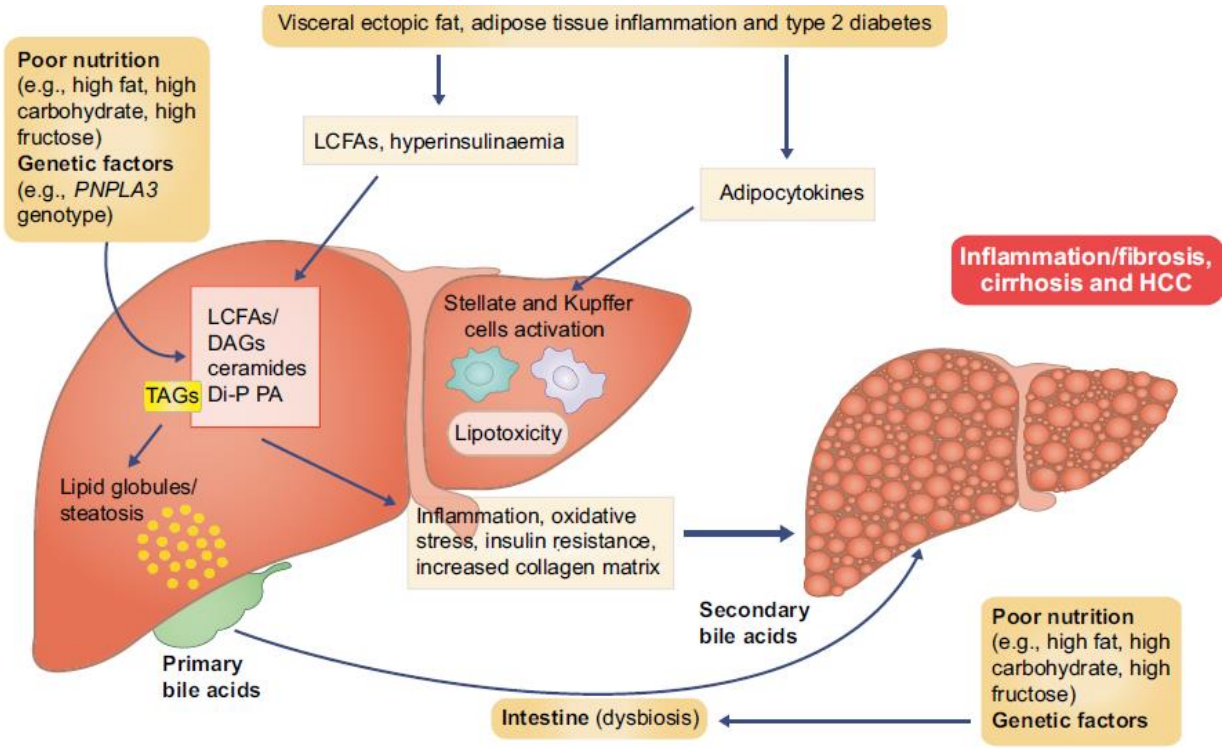
5.Hypogonadism

6.Pancreato-duodenal resection



PRIMARY AND SECONDARY RISK FACTORS FOR NAFLD

COMMON PATHOGENIC MECHANISMS FOR NAFLD



“Hepatic steatosis is a prerequisite to making a histological diagnosis of NAFLD . Several mechanisms may lead to steatosis, including (1) increased fat supply such as high-fat diet and excess adipose lipolysis; (2) decreased fat export in the form of very low density lipoprotein-triglyceride; (3) decreased free fatty β-oxidation; and (4) increased *de novo* lipogenesis (DNL) . Certain cytokines derived from inflammation sites, particularly from extrahepatic adipose tissues, can trigger steatosis.. In addition, the enhancement of hepatic DNL is deemed to be a unique feature in steatosis. Insulin resistance is responsible for the massive metabolic dysregulations of NAFLD that initiate and aggravate hepatic steatosis. At a certain point, the simple steatosis transforms to steatohepatitis in about 20–30% of NAFLD patients.This breakthrough-like process is mediated by the interplay of multiple hit factors”.

ADIPOSE TISSUE INFLAMMATION *:*

“Hypoxia and death of rapidly expanding adipocytes are responsible for adipose tissue inflammation.. Adipocytes under inflammation secrete cytokines and chemokines, particularly tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and CC chemokine ligand-2 (CCL2) . TNF-α is involved in the regulation of insulin resistance. IL-6 is derived from many cells including adipocytes and IL-6 have been shown to regulate hepatic insulin resistance via upregulation of SOCS3, a suppressor of cytokine signaling.

CCL2 recruits macrophages to the adipose tissue, resulting in even more local cytokine production and perpetuating the inflammatory cycle; TNF-α and IL-6 induce a state of insulin resistance in adipocytes, which stimulates triglyceride lipolysis and fatty acid release into the circulation. At the same time, extrahepatic adipocytes are compromised in their natural ability to secrete adiponectin, an anti-inflammatory adipokine that facilitates the normal partitioning of lipid to adipocytes for storage . Circulating adiponectin regulates hepatic fatty β-oxidation through AMP-activated protein kinase (AMPK) and acetyl-CoAcarboxylase (ACC) signaling. Together, these abnormalities accentuate fat loss from adipocytes and promote ectopic fat accumulation."

DE NOVO LIPOGENESIS (DNL):

"Diets enriched in both saturated fat and simple sugar carry a high risk of hepatic steatosis, through enhanced DNL . Since carbohydrates are substrates for DNL, the amount of carbohydrate in the diet will positively influence the amount of DNL in the liver. Simple sugars are converted to fatty acids more readily than complex carbohydrates and fructose is a more potent inducer of DNL than glucose . Dietary fat, particularly saturated fat, stimulates DNL by upregulating SREBP-1 (sterol responsive element binding protein), a key regulator of the lipogenic genes in the liver."

INSULIN RESISTANCE:

“Insulin resistance is caused by variety of factors, including soluble mediators derived from immune cells and/or adipose tissue, such as TNF-α and IL-6 . Serine phosphorylation of insulin receptor substrates by inflammatory signal transducers such as c-jun N-terminal protein kinase 1 (JNK1) or inhibitor of nuclear factor-κB kinase-β (IKK-β) is considered one of the key aspects that disrupts insulin signaling. Insulin resistance is characterized not only by increased circulating insulin levels but also by increased hepatic gluconeogenesis, impaired glucose uptake by muscle, and increased release of free fatty acids and inflammatory cytokines from peripheral adipose tissues , which are the key factors promoting accumulation of liver fat and progression of hepatic steatosis” .

LIPOTOXICITY:

“Long-chain saturated fatty acids (SFAs) such as palmitate (C16:0) and stearate (C18:0) are toxic to liver. Under physiological conditions, SFAs are transported to mitochondria for β-oxidation or esterified for either excretion in the form of VLDL (very low density lipoproteins) or storage as lipid droplets. Free cholesterol accumulation leads to liver injury through the activation of intracellular signaling pathways in Kupf fer cells (KCs), hepatic stellate cells (HSCs), and hepatocytes. The activation of KCs and HSCs promotes inflammation and fibrogenesis . Excessive SFA,can activate a variety of intracellular

responses such as JNK1 and a mitochondrial death pathway, resulting in lipotoxic stress in the endoplasmic reticulum and mitochondria, respectively . In addition, the toll like receptor 4 (TLR4) is a pattern recognition receptor that activates a proinflammatory signaling pathway in response to excessive SFAs. This pathway is initiated by recruiting adaptor molecules such as toll/IL-1 receptor domain containing adaptor protein (TIRAP) and myeloid differentiation factor88(MyD88) that ultimately lead to activation of nuclear factor κB with production of TNF-α ."

MITOCHONDRIAL DYSFUNCTION*:*

"Multiple studies have shown that liver ATP levels are decreased in NAFLD . This implicates mitochondrial dysfunction in the state of liver fat overload that is characteristic of NAFLD. Reduced enzymatic activities of mitochondrial electron transport chain (ETC) complexes attributes to increased generation of reactive oxygen species (ROS) as a result of ETC leakage during mitochondrial β-oxidation in energy production . ROS can damage the ETC and even cause mutations in the mitochondria DNA."

OXIDATIVE STRESS*:*

"Increased supply of fatty acids to hepatocytes, leads to oxidative stress due to raised levels of reactive oxygen/nitrogen species (ROS/RNS) and lipid peroxidation that are

generated during free fatty acid metabolism in microsomes, peroxisomes, and mitochondria . Peroxidation of plasma and intracellular membranes may cause direct cell necrosis/apoptosis and mega mitochondria, while ROS-induced expression of Fas-ligand on hepatocytes may induce cell death".

ENDOPLASMIC RETICULUM (ER) STRESS*:*

"Under stressful conditions such as NASH, it has been observed that ER efficiency in the protein folding, repairing, and/or trafficking machinery is decreased while the demand of protein synthesis and folding/repair is increased . Such an imbalance is termed ER stress, which can lead to the accumulation of unfolded and/or misfolded proteins within the ER lumen.This type of cellular stress usually triggers an adaptive response, aimed at resolving ER stress, called unfolded protein response (UPR) ."

"The UPR is mediated by at least three different stress-sensing pathways: protein kinase RNAlike ER kinase (PERK), inositol-requiring protein 1α (IRE1α), and activating transcription factor 6 (ATF6) . Coupled with inflammation, oxidative stress, insulin resistance, and apoptosis signaling, hepatic ER stress seems to play an important role in regulating the composition and size of lipid droplets as well as lipid synthesis, including cholesterol metabolism , through SREBP."

MICROBIOTA ASSOCIATED MECHANISMS OF NAFLD

“Gut microbiota may contribute to the pathogenesis of NAFLD through several mechanisms,

(1) increased production and absorption of gut short-chain fatty acids;

(2) altered dietary choline metabolism by the microbiota;

(3) altered bile acid pools by the microbiota;

(4) increased delivery of microbiota derived ethanol to liver;”

“(5) gut permeability alterations and release of endotoxin; and

(6) interaction between specific diet and microbiota

(7) chronic kidney disease may mutually aggravate NAFLD and associated metabolic disturbances through multiple paths including altered intestinal barrier function and microbiota composition.”

GENETIC FACTORS:

In NAFLD, two genes (*PNPLA3* and *TM6SF2*) have been identified as potential genetic modifiers.

PNPLA3 (PATATIN-LIKE PHOSPHOLIPASE DOMAIN CONTAINING3*).*

*“*The *PNPLA3* gene (adiponutrin) encodes a transmembrane polypeptide chain exhibiting triglyceride hydrolase activity , which is highly expressed on the endoplasmic reticulum and lipid membranes of hepatocytes and adipose tissue . The encoded protein has retinyl esterase activity and allows retinol secretion from hepatic stellate cells while the mutation causes intracellular retention of this compound . The association between

the *PNPLA3* variant and steatosis or severity of histological liver disease has been widely observed The link between *PNPLA3* I148M variant and NAFLD is independent of metabolic syndrome (MS) and its features; that is, most of patients carrying this variant are not associated with obesity, diabetes, and atherogenic dyslipidemia. Furthermore, the *PNPLA3* genotype seems to also influence steatosis development in patients with hepatitis B and hepatitis C and alcohol abuse, and it has been independently associated with the progression of hepatitis, including fibrosis, cirrhosis, and HCC .The association between the *PNPLA3* variant I148M and the risk of HCC development has been robustly validated in patients with NAFLD."

TM6SF2 (TRANSMEMBRANE 6 SUPERFAMILY MEMBER 2):

"Silencing of the gene showed a 3-fold increase in hepatic triglycerides levels and a decrease in plasma levels of triglycerides, LDL- and high density lipoprotein- (HDL-) cholesterols, and very low density lipoprotein (VLDL). *TM6SF2* gene regulates hepatic triglyceride secretion and that the functional impairment of *TM6SF2* promoted NAFLD."

CLINICAL FEATURES

"Fatty liver is usually a asymptomatic condition. It is the incidental finding in most of the patients. In symptomatic patients , they present with right upper quadrant pain , malaise , fatigue and bloating. There may be associated hepatomegaly and one or more components of metabolic syndrome may be present. Presence of liver cell failure like

ascites , palmar erythema , spider angioma indicates associated cirrhosis. Splenomegaly may be present in small percentage of individuals.”

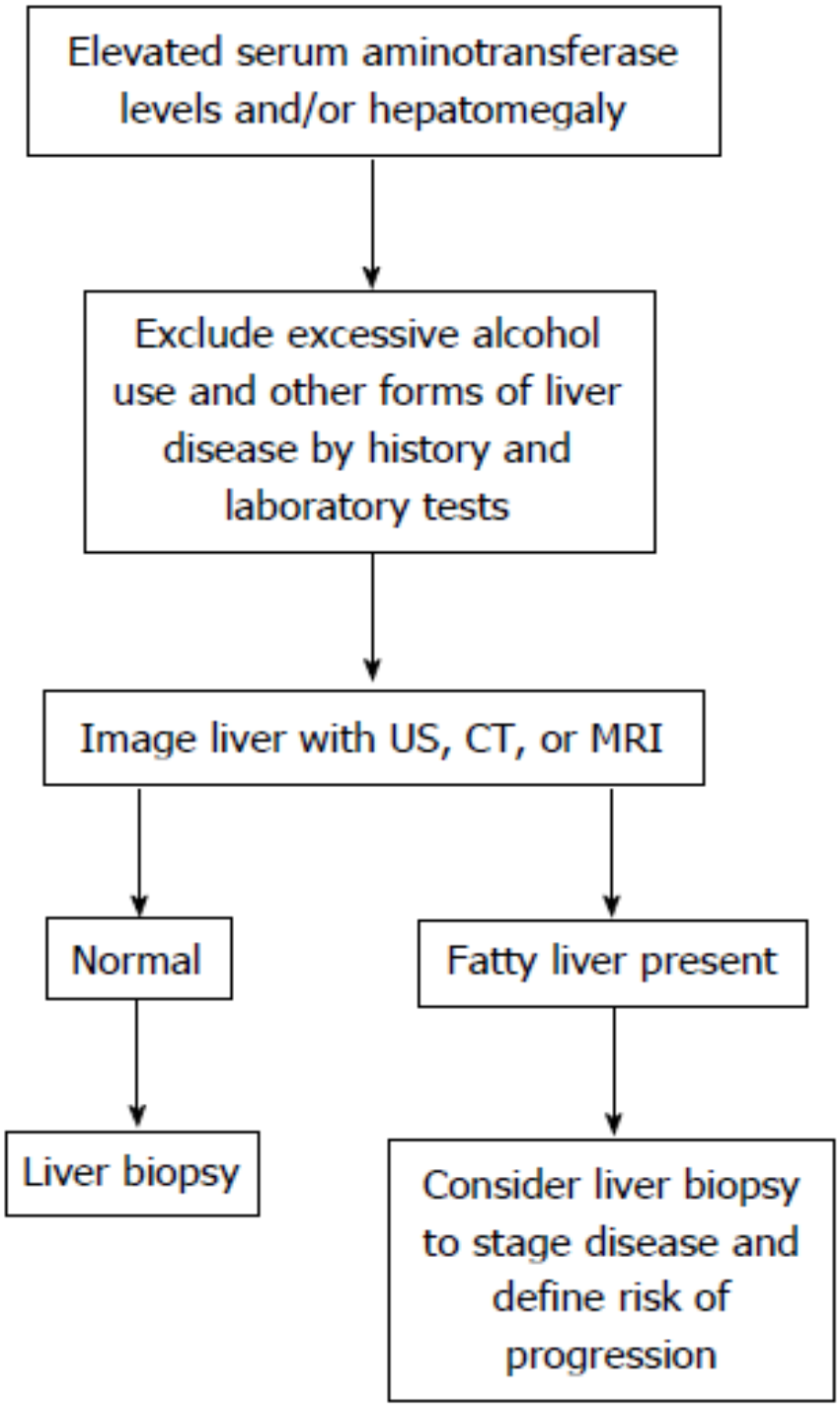
DIAGNOSIS OF NAFLD:

The diagnosis of NAFLD requires that

(a) there is hepatic steatosis by imaging or histology,

(b) there is no significant alcohol consumption,

(c) there are no competing etiologies for hepatic steatosis, and (d) there are no co-existing causes for chronic liver disease.



DIAGNOSTIC APPROACH

LABORATORY FEATURES OF NAFLD

"Suspicion for NAFLD is triggered by abnormalities of liver chemistry tests that are usually performed for non liver-related reasons. About 50% of patients with simple steatosis have higher liver biochemical test levels, which occur in 80% of patients with advanced NAFLD. Also, serum aspartate aminotransferase or ALT level, or both is usually increased up to 1.5- to 4-fold and levels rarely exceed 10 times the upper limit of normal. However, the gamma glutamyl transpeptidase and alkaline phosphatase levels may be elevated, but the serum prothrombin time, bilirubin level and serum albumin level are normal, except in patients with NAFLD-associated cirrhosis. Serum ferritin level may be higher in 20% to 50% of NAFLD patients and can be considered a marker for advanced disease. Hyperglycemia and dyslipidemia may be detected in 30% to 50% of NAFLD subjects. Laboratory and clinical findings do not correlate with NAFLD histologic severity."

IMAGING FEATURES OF NAFLD

"The radiologic features of fatty liver disease stem from the increased fat content of the liver parenchyma. The spatial pattern may be diffuse and homogeneous or heterogeneous, with focal fat deposition in an otherwise normal liver or areas of focal fat sparing in a diffusely fatty liver. The homogeneous form is the most common; the heterogeneous and focal forms may simulate perfusion abnormalities, diffusely infiltrative disease, nodular lesions, or masses. The most important modalities used in the assessment of hepatic

steatosis are ultrasonography, computed tomography (CT), and magnetic resonance (MR) imaging and MR spectroscopy."

"Transabdominal ultrasonography is the most common imaging technique to diagnose hepatic steatosis due to its widespread availability, noninvasiveness and low cost. At ultrasonography, diffuse fatty liver is characterized by hyperechogenicity of the liver parenchyma relative to the adjacent right kidney or spleen (the so-called bright liver). Focal fat deposition appears as a hyperechoic area in an otherwise normal liver, whereas focal fat sparing is represented by a hypoechoic area within diffusely hyperechoic liver parenchyma. Other ultrasound features of fatty liver include decreased visualization of vascular margins, attenuation of the ultrasound beam, loss of definition of the diaphragm, and hepatomegaly ."

USG GRADING OF HEPATIC STEATOSIS:

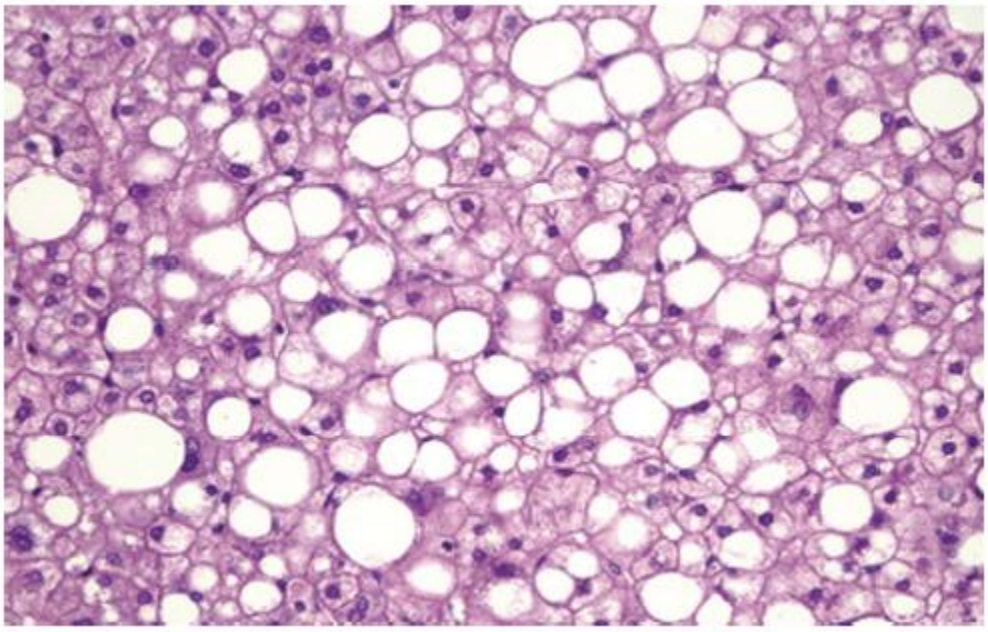
"GRADE 1 (mild) : normal visualization of diaphragm / intrahepatic vessels.
GRADE 2(moderate): impaired visualization of diaphragm/intrahepatic vessels.
GRADE 3 (severe) : poor visualization of diaphragm/intrahepatic vessels."

"Transient elastography, a recently developed technique based on ultrasound monitoring of the passage of a low frequency pressure wave through tissues, has been found to be a promising non-invasive technique for the detection of advanced fibrosis caused by

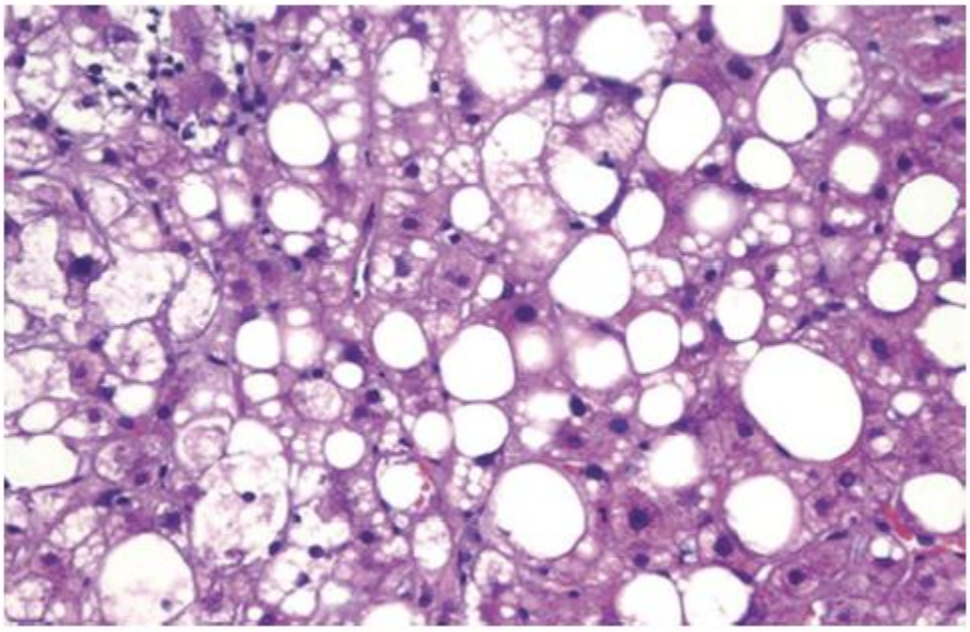
chronic viral hepatitis and NASH, although abdominal obesity may compromise its utility in the NASH patient population."

HISTOLOGICAL FEATURES OF NAFLD

"The main histologic features of NAFLD are similar to those of alcohol-induced liver disease and include steatohepatitis (fatty liver plus parenchymal inflammation with or without accompanying focal necrosis), steatosis (fatty liver) and varying degrees of fibrosis, including cirrhosis. Steatosis is predominantly macrovesicular and usually is distributed diffusely throughout the liver lobule, although prominent microvesicular steatosis and zone 3 (perivenular) steatosis have been reported . Mild neutrophilic, lymphocytic, or mixed inflammatory infiltrates also may be observed, and glycogenated nuclei are common. NASH, which is an advanced form of NAFLD, is indistinguishable histologically from alcoholic hepatitis ."



SIMPLE STEATOSIS



NON ALCOHOLIC STEATOHEPATITIS

GRADE 1, MILD

Steatosis: predominantly macrovesicular, involves < 33 up to 66% of the lobules

Ballooning: occasionally observed; zone 3 hepatocytes

Lobular inflammation: scattered and mild acute (polymorphs) inflammation and occasional chronic inflammation (mononuclear cells)

Portal inflammation: none or mild

GRADE 2, MODERATE

Steatosis: any degree and usually mixed macrovesicular and microvesicular

Ballooning: obvious and present in zone 3

Lobular inflammation: polymorphs may be noted associated with ballooned hepatocytes, pericellular fibrosis; mild chronic inflammation may be seen

Portal inflammation: mild to moderate

GRADE 3, SEVERE

Steatosis: typically > 66% (panacinar); commonly mixed steatosis

Ballooning: predominantly zone 3; marked

Lobular inflammation: scattered acute and chronic inflammation; polymorphs may appear concentrated in zone 3 areas of ballooning and perisinusoidal fibrosis

Portal inflammation: mild or moderate

Steatosis: grade 1 = 0–33%, 2 = 33%–66%, 3 = >66%

Ballooning: zonal location noted and severity (mild or marked) recorded according to estimate of numbers of hepatocytes involved

Lobular inflammation: 0–3 based on observations of foci per 20 × field; 1 = 1–2 foci, 2 = up to 4 foci, 3 = > 4 foci. In addition, cell types (acute or chronic) and location were noted

Portal inflammation: 0–3, 1 = mild, 2 = moderate, 3 = severe

STAGING FIBROSIS IN NASH

Stage 1: Zone 3 perivenular perisinusoidal/pericellular fibrosis, focal or extensive

Stage 2: As above with focal or extensive periportal fibrosis

Stage 3: Bridging fibrosis, focal or extensive

Stage 4: Cirrhosis

HISTOLOGICAL GRADING FOR NASH

“The standardized schema of NAFLD staging and grading was published by Brunt and associates in 1999, who assigned the overall grade of mild, marked, or severe (grades 1, 2, and 3, respectively), based on the degree of ballooning degeneration, steatosis and lobular and portal inflammation.”

NON INVASIVE TESTS

“1. Fibro test – estimates serum haptoglobin , total bilirubin , α2 macroglobulin , apolipoprotein A1 and GGTP.

2. necro inflammatory activity index – estimates above mentioned markers and ALT.

3. NAFLD FIBROSIS SCORE – Age ,BMI , AST/ALT ratio , platelet count and serum albumin.

4. Fibroscan

5.Serum Dehydroepiandrosterone

6.Serum hyaluronic acid.”

DIFFERENTIAL DIAGNOSIS:

Table 5: CAUSES OF HEPATIC STEATOSIS

Macrovesicular steatosis

- Excessive alcohol consumption
- Hepatitis C (genotype 3)
- Wilson's disease
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- Medications (e.g. amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

- Reye's syndrome
- Medications (valproate, anti-retroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g. LCAT deficiency, cholesterol ester storage disease, Wolman disease)

NAFLD AND METABOLIC SYNDROME:

“Metabolic syndrome, (Syndrome X) or insulin resistance syndrome is defined as a group of metabolic abnormalities with insulin resistance and abdominal obesity.There is relationship between metabolic syndrome and NAFLD.This is reflected by the fact that more than 90% of those with NAFLD have one or more features of metabolic syndrome and 33%have three or more features.”

“Insulin resistance is the main component of metabolic syndrome, which favours compensatory hyperinsulinemia by increased production in the pancreatic beta cells and decreased degradation in the liver.Since the same pathophysiological features apply in the development of NAFLD,it is now considered as the hepatic component of metabolic syndrome. The presence of metabolic syndrome leads to progressive and severe liver disease increasing the likehood of developing NASH and cirrhosis.”

NAFLD AND OBESITY:

“Obesity is defined as abnormal and excessive accumulation of fat that poses a risk to health . BMI is a simple index used to classify overweight and obesity. It is defined as a person’s weight in kilograms divided by the square of his height in metre (kg/ sq,m) . it can also be measured by triceps skin fold thickness , midarm circumference , waist circumference and waist hip ratio. Visceral fat can be assessed by CT and MR spectroscopy.”

“Fat distribution in the body plays a pivotal role in the complications and morbidity . visceral fat and abdominal fat are given particular importance in this regard . visceral fat is biologically more active , high lipolytic activity and secretes adipocytokines . hence there is more production of fatty acids and glycerol which reach the liver through the portal vein and lead to steatosis . subcutaneous fat has less adipocyte activity than visceral fat. Obesity associated inflammation recruits macrophages into cells inducing endoplasmic stress and making the cell resistant to insulin . macrophages are more in number in visceral fat and promote insulin resistance.”

“Complex humoral and neural mechanisms are involved in the pathogenesis of obesity. Leptin is synthesized in fat cells in response to abundant fat stores which stimulates physical activity , energy production and heat production . adiponectin , another adipocytokine directs fatty acids to muscle for oxidation . Any alteration in these process

leads to obesity. Gherlin is another gut hormone which increases food intake , whose post prandial suppression when attenuated leads to obesity.”

Table 1 Common definitions for metabolic syndrome

Criterion	NCEP ATP III[6] (3 or more criteria)	IDF[40] (abdominal obesity plus 2 or more other criteria)
Abdominal obesity		
Men	> 40 inches	≥ 37 inches
Women	> 35 inches	≥ 31.5 inches
Hypertriglyceridemia	≥ 150 mg/dL	≥ 150 mg/dL
Low HDL		
Men	< 40 mg/dL	< 40 mg/dL
Women	< 50 mg/dL	< 50 mg/dL
Hypertension	≥ 130/85 mm Hg or on antihypertensive medication	≥ 130/85 mm Hg
Impaired fasting glucose or diabetes	≥ 110 mg/dL* or taking insulin or hypoglycemic medication	≥ 100 mg/dL

NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; IDF, International Diabetes Federation; HDL, high-density lipoprotein.
*Recently lowered to 100 mg/dL.[13]

Metabolic Syndrome Criteria for Asian Indians*

Risk factor	Defining level
Abdominal obesity	**Waist**
Men	>90 cm/ 35.4 inches
Women	>80 cm/ 31.5 inches
Triglycerides	≥150 mg/dL
HDL-C	
Men	<40 mg/dl
Women	<50 mg/dl
Blood Pressure	≥130/≥85 mm Hg
Fasting glucose	≥100 mg/dl

WC for Americans is 102cm for men and 88cm for women
Alberti KG. *Circulation*. Oct 20 2009;120(16):1640-1645.

NAFLD AND ATHEROSCLEROSIS:

“Atherosclerosis is defined as loss of elasticity of the arterial wall and associated with thickening . it can affect any vessel in the body including those supplying the heart leading to coronary artery disease , brain resulting in stroke and peripheral arteries. It is considered to be the major cause of death and premature morbidity in developed countries. Atherosclerosis is considered to be a slow process which evolves over years. The initiating event is the endothelial injury . Endothelial injury can be caused by various factors that in turn leads to endothelial dysfunction.”

“Endothelial dysfunction is considered to be one of the initial components of the inflammatory process that results in atherosclerosis. It is characterized by impaired endothelial relaxation , increased vascular permeability and increased expression of the circulating adhesion molecules. This derangement leads to accumulation of lipoproteins in the initima of major arteries which forms the precursor for atherosclerotic plaque , **fatty streak**.”

“These lipoproteins trigger local inflammatory response giving rise to recruitment of mononuclear cells into the intima. The mononuclear cells elaborate a number of cytokines that stimulate smooth muscle proliferation and production of extracellular matrix leading to the complex atherosclerotic lesion . the products of coaguulaion and thrombosis complicate further process.”

“Dyslipidemia is one of the established risk factors for atherosclerosis . atherogenic dyslipidemia is considered when there is a combination of raised triglycerides , low levels of HDL c with apoliprotein B , small dose LDL and small HDL particles. Apart from the established risk factors , lipoprotein (a) , prothrombotic factors , homocysteine , proinflammatory factors and impaired fasting glucose are proposed to be emerging risk factors for atherosclerosis.”

NAFLD AND CARDIOVASCULAR DISEASE :

“The CVD is characterized by critically narrowing (stenosis) or occlusion (atherothrombosis) of blood vessels. Key processes in CVD are endothelial dysfunction, atherosclerosis, and impaired regulation of coagulation and fibrinolysis. The complement system may be involved in all these processes based on its immune, inflammatory and metabolic functions. Systemic complement levels may be involved in coagulation and fibrinolysis, which together with endothelial dysfunction and atherosclerosis result in cardiovascular disease.The complement-C3 has shown independent associations with insulin resistance, liver dysfunction and in the risk of Metabolic Syndrome and T2DM.

Circulating levels of several inflammatory markers (C reactive protein, interleukin-6, monocyte chemotactic protein 1, and TNF-a), procoagulant factors (plasminogen activator inhibitor 1, fibrinogen, and factor VII), and oxidative stress markers are highest in patients with NASH independent of obesity and other potentially confounding factors. NAFLD seems to be not simply a marker of cardiac and arrhythmogenic complications

but also may play a part in their pathogenesis possibly *via* atherogenic dyslipidemia and the hepatic secretion of several pathogenic mediators".

"Central obesity can provoke inflammation and insulin resistance in adipose tissue and the release of proinflammatory adipokines and Free Fatty Acids (FFAs). Liver fat is associated with an increased number of higher small dense LDL (sdLDL) particles, which have higher atherogenic properties than larger less dense LDL-C particles. These lipoproteins are associated with increased activity of hepatic lipase favoring the production of sdLDL particles. Patients with NASH can have the transcriptional regulation of proatherogenic genes altered and it is associated with the activation of molecular events that may also be responsible for the local production of mediators or modifiers of circulatory homeostasis."

"The atherogenecity of the increase in sdLDL is likely to be further compounded by decrease in LDL receptor expression in NASH.From a cardiovascular point of view the direct relation between LDL-C and HMGCR expression suggests that the liver disease contributes to LDL-mediated cardiovascular risk."

NAFLD, CARDIAC ARRHYTHMIAS AND AORTIC VALVE SCLEROSIS

"Recently, mildly elevated liver transaminases have been shown to be independently associated with increased incidence of atrial fibrillation (AF) in the Framingham Heart

Study cohort . Finally, the presence of aortic valve sclerosis, i.e., a progressive disease that shares multiple pathogenic risk factors with CVD and is associated with an increased risk of CVD mortality has also been linked with NAFLD, independently of established CVD risk factors, in both diabetic and nondiabetic individuals."

"Therefore the liver represents a contributor to systemic inflammatory changes, insulin resistance and hyperlipidemia determining a progression of vascular diseases and atherosclerosis. NAFLD/NASH are associated with an increased risk of incident cardiovascular disease, independently of the traditional risk factors."

"NAFLD patients have significantly higher carotid artery intima-media thickness (IMT), a marker of subclinical atherosclerosis, comparing with those without fatty liver impaired endothelial function, and lower concentrations of adiponectin. IMT is strongly associated with degree of hepatic steatosis, necro inflammation, and fibrosis among NAFLD patients"

" NAFLD patients have strong association with early carotid atherosclerosis, independent of classical risk factors,insulin resistance, and the presence of metabolic syndrome. Plasma concentrations of high-sensitivity C-reactive protein (hs-CRP), fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) with biopsy-proven NASH. Also, the highest concentrations of adiponectin were found in biopsy proven

NAFLD.Abnormal left ventricular energy metabolism, fat accumulated in the epicardial area despite normal left ventricular morphological features, and systolic and diastolic function.”

NAFLD AND DIABETES MELLITUS:

“NAFLD is strongly associated with T2DM and cardiovascular disease (CVD). It is characterized by insulin resistance and mitochondrial dysfunction . There is a gradual increase in the severity of insulin resistance in the range of NAFLD which may contribute to the evolution of liver damage. Also, is associated with an increased risk of kidney disease in subjects with multiple CVD risk factors and tends to be considered as an independent CVD marker. Diabetes, dyslipidemia, hypertension and CVD coexist more frequently in individuals with NAFLD”

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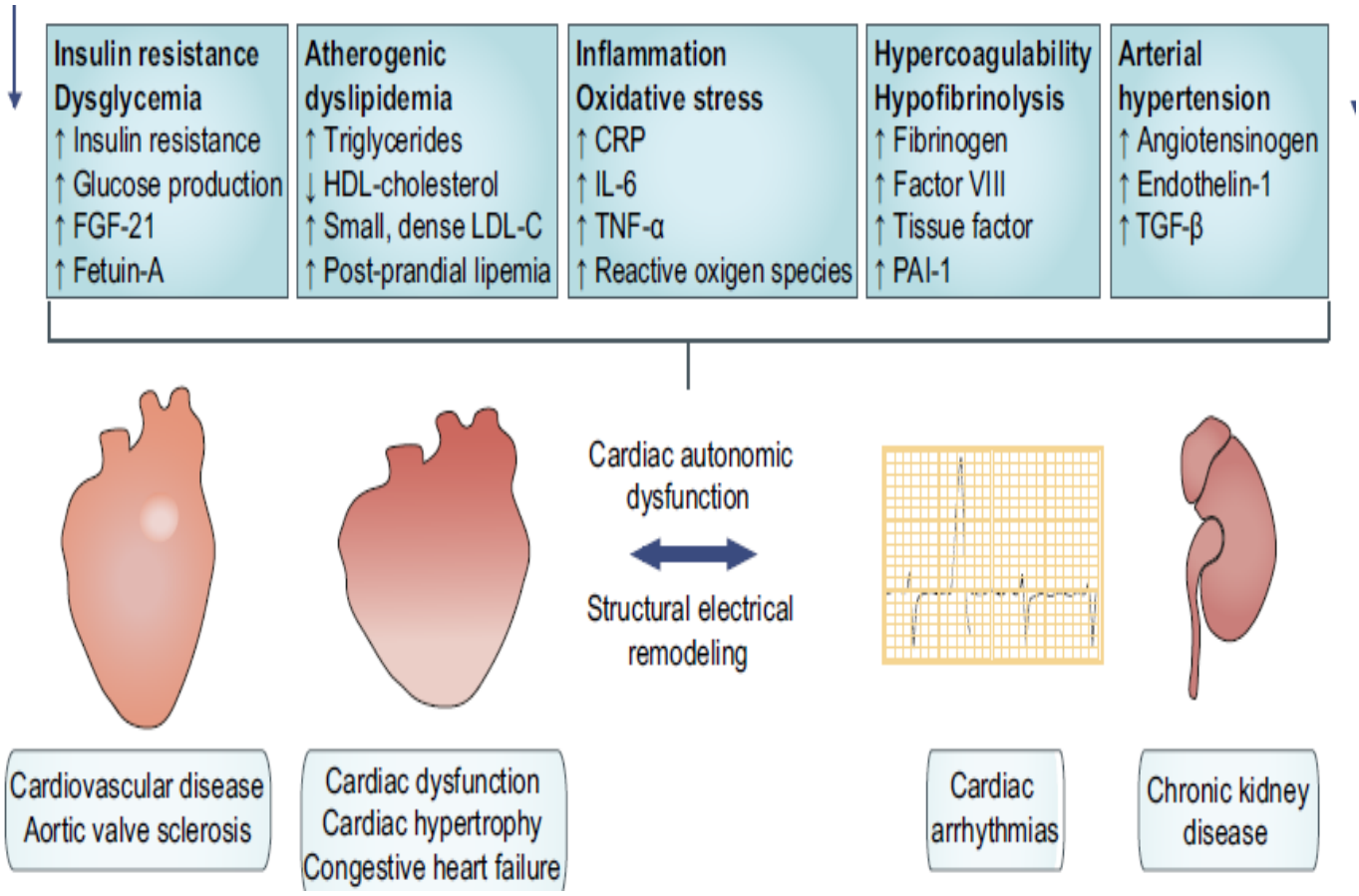


putative mechanisms underlying the contribution of NAFLD to the increased risk of cardiovascular disease (CVD), chronic kidney disease (CKD) and other structural and arrhythmic cardiac complications

DIET AND NAFLD:

“Change in dietary pattern plays a crucial role in the exponentially increasing incidence of obesity. The use of refined carbohydrates produces more energy per serving at the expense of causing hyperinsulinemia. Increase in dietary fat produces more calories per gram , presence of trans fat improves the taste but are not metabolized in the body.

The presence of dietary fibres decreases post prandial insulin surge and lipogenesis . but dietary fibre consumption had reduced over the recent years contributing to obesity . The use of monosodium glutamate enhances taste and flavor in foods have been found to increase appetite. Fructose in fruit and soft drinks inhibits the suppression of gherlin and delays satiety. It is also converted to fructose 1 phosphate without regulation leading to lipogenesis , fatty liver and insulin resistance.”

MANAGEMENT STRATGIES:

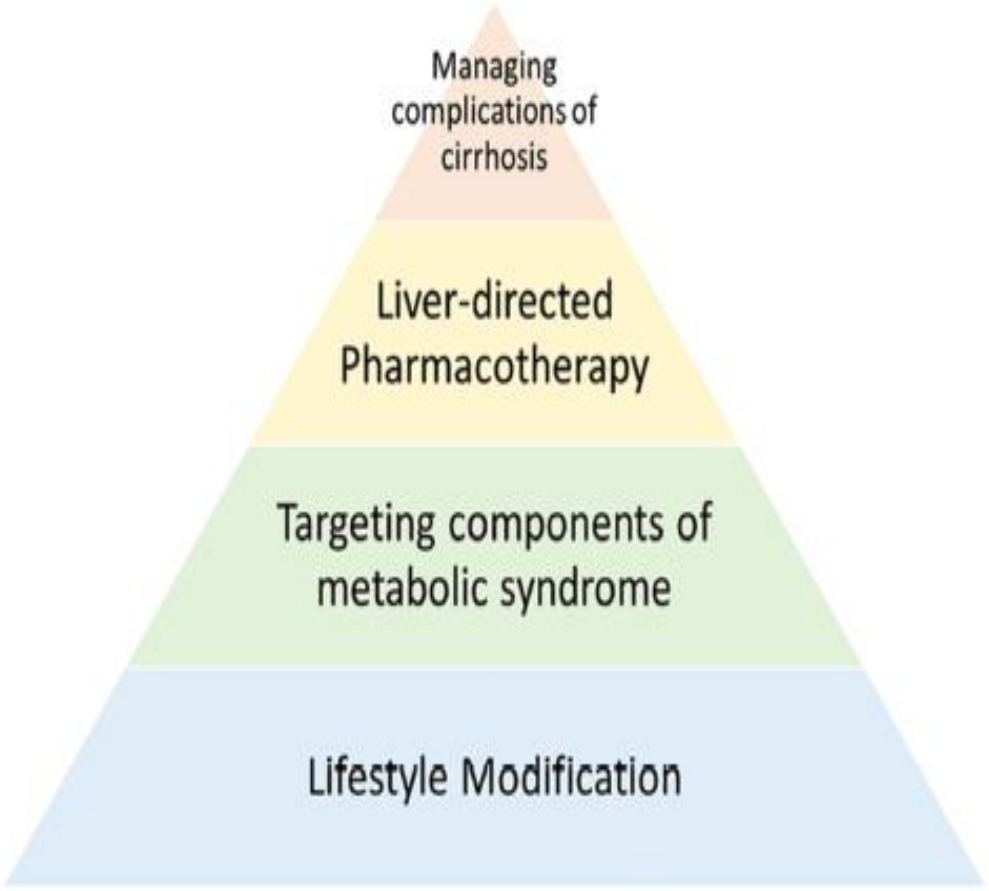


Figure 1 Management strategies in non-alcoholic fatty liver disease (NAFLD).

TREATMENT OPTIONS FOR NAFLD:

Treatment	Intervention/indication
Diet	Calorie restricted diet (600 calories less than daily requirement)
	Aim to lose 0.5–1.0 kg/week[11]
	Avoid saturated fats, simple carbohydrates and sweetened drinks
	Aim to lose >10% body weight and maintain loss
Exercise	Increasing physical activity
	Reduce total sedentary time
	30 min moderate exercise 5×/week
	'Aerobic', 'resistance' and 'high intensity' exercise are all effective
	Aim >10 000 steps/day (pedometer)
Orlistat (enteric lipase inhibitor)	Achieve weight loss in conjunction with lifestyle modification if BMI>30 kg/m^2[11]
	Only continue if >5% loss of body weight in 3 months is achieved
Bariatric surgery	Not a primary treatment for NASH
	Treatment for obesity if BMI >40 kg/m^2 or between 35 and 40 kg/m^2 with other significant disease[11]
	Consider as first-line option if BMI greater >50 kg/m^2[11]

Pioglitazone	Recommended for patients with more aggressive NASH who have failed lifestyle interventions
Vitamin E	Reserved for selected patients with more advanced precirrhotic NASH who have failed lifestyle interventions

TREATMENT OF TYPE 2 DIABETES AND METABOLIC SYNDROME IN NAFLD PATIENTS:

Treatment	Indication
Dietary intervention	See table 1
Metformin	First-line treatment of T2DM
Pioglitazone	Second-line treatment of T2DM in NASH
GLP-1 analogue	Third-line treatment of T2DM in NASH
Insulin/sulfonylureas	Fourth-line treatment of T2DM in NASH

MANAGEMENT OF HYPERTENSION AND DYSLIPIDEMIA IN NAFLD PATIENTS:

Risk factor	Treatment/indication
Hypertension	ACEI and ARBs first-line if BP >140/90 mm Hg[61] Escalate treatment according to NICE hypertension guidelines
Dyslipidaemia	Primary prevention with statin if ≥20% 10-year risk of developing cardiovascular disease[66] If secondary prevention, aim total cholesterol <4 mmol/L

AIM AND OBJECTIVES OF OUR STUDY:

1.To assess the association of MPV in NAFLD patients.

2.To investigate whether this increased MPV is associated with increased cardiovascular disease in patients with NAFLD .

MATERIALS AND METHODS;

STUDY POPULATION:

The present study is going to be conducted on patients admitted in MGE/Medicine wards or attending outpatient departments of Government Rajaji Hospital, Madurai during the period of March2016 to August2016.

INCLUSION CRITERIA:

"Age>18 yrs

Hepatosteatosis proven by USG abdomen

No medication history

No alcohol consumption

No viral hepatitis."

EXCLUSION CRITERIA:

“Alcohol consumption more than 40 g/wk.

Viral hepatitis.

Hepatotoxic drugs.

Women on OCP.

Autoimmune hepatitis.

Metabolic Liver disease.

Pregnancy.

Hepatobiliary surgery”

ANTICIPATED OUTCOME:

Patients with NAFLD have increased MPV and this is associated with increased cardiovascular risk.

METHODS:

“A previously designed proforma was used to collect the demographic and clinical details of the patients. All the patients will undergo detailed clinical evaluation, appropriate investigations.”

“History was taken on details ofalcohol consumption,blood transfusion ,IV drug abuse,diabetes mellitus, use of medications. Fasting blood sugar, liver function tests including serumbilirubin, serum transaminases,viralmarkers,fasting lipid profile was estimated.Degree of hepatosteatosis was evaluated by ultrasound scan and from laboratory data of patients with NAFLD obtained at the time of diagnosis.”

LABORATORY INVESTIGATIONS:

1.Blood sugar

2. platelet count.

3.Liver enzymes and viral markers.

4. Fasting lipid profile.

5.Mean platelet volume.

“For the above mentioned hematological parameter , 2 ml of blood was withdrawn by venepuncture from the patients within 24 hours of admission to the hospital. The venepuncture site was properly cleaned and blood withdrawn and collected in EDTA containing disposable tubes . the sample was transported immediately to qualified controlled centre where the sample was analysed for platelet volume. The instrument used for analysis was COBAS MICROS OT 18 automated hematological analyser made by ROCHE.”

“The instrument was started up . after starting , a pipette appeared from the instrument . blood sample was fed to the instrument by the principle worker . the pipette draw the necessary amount of blood and withdrew on its own after taking necessary amount of blood . from that moment a waiting period of 180 seconds appeared on the screen. At the end of 180 seconds , a print out with the platelet count and mean platelet volume was ejected from the printer connected to the instrument. The instrument was repeatedly standardized for quality control”.

STASTICAL ANALYSIS:

“The data collected during the study was formulated into a master chart in Microsoft office excel and statistical analysis was done with help of computer using stastistical software packages SPSS V.17 software.”

DESIGN OF STUDY:

Cross sectional study

PERIOD OF STUDY:

March2016 To August 2016 (6 months)

COLLABORATING DEPARTMENTS:

Department of Medical gastroenterology.

Department of Biochemistry

Department of Microbiology.

Department of Radiology.

Department of Pathology.

ETHICAL CLEARANCE:

Necessary ethical clearance was obtained from the ethical committee, GRH , Madurai.

CONSENT:

Individual written and informed consent.

ANALYSIS:STATISTICAL ANALYSIS.

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: SELF

PARTICIPANTS:

The present study was conducted on patients admitted in MGE/Medicine wards or attending outpatient departments of Government Rajaji Hospital, Madurai during the period of March 2016 to August 2016.

OBSERVATIONS AND RESULTS :

TABLE 1 : AGE DISTRIBUTION IN NAFLD

AGE	NO OF CASES
<40	13
41-50	43
51 - 60	32
> 60	12
Total	100
Mean	49.21

Among 100 patients, 56% of patients age lies between 40 to 50 years.

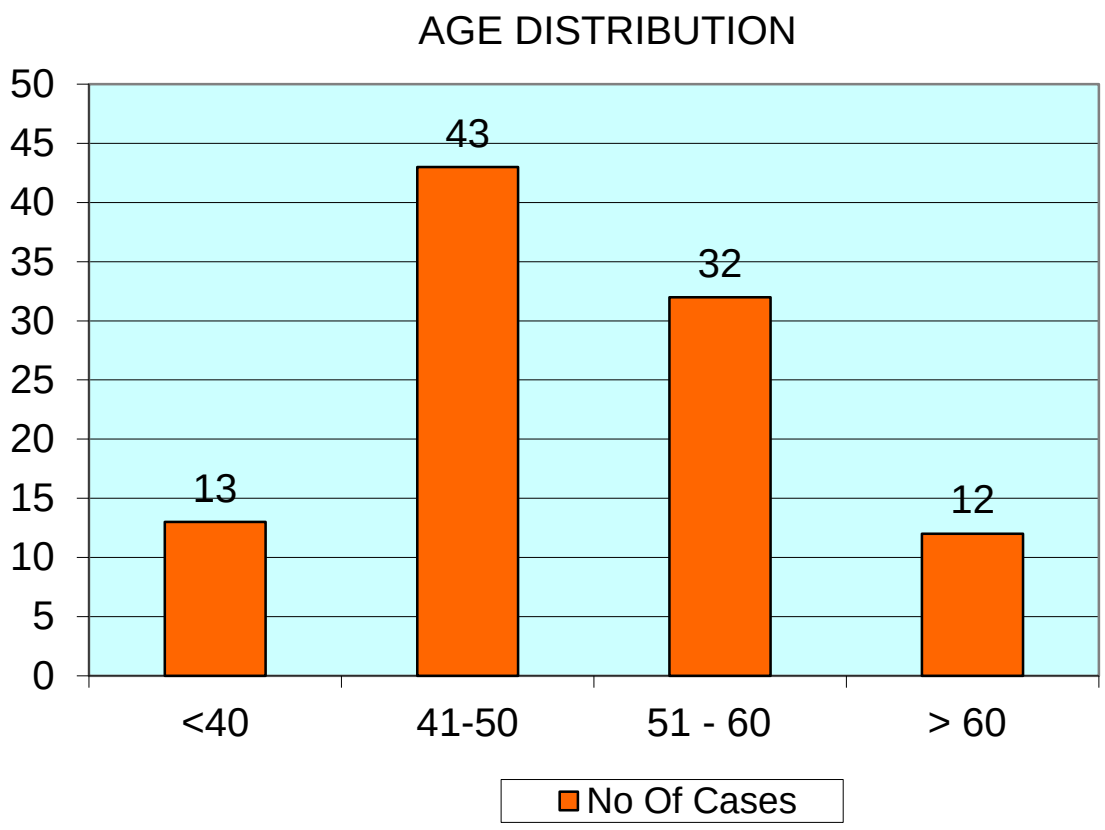


TABLE 2 SEX DISRTIBUTION:

SEX	NO OF CASES
Male	72
Female	28
Total	100

Among 100 patients 72% were males and 28% were females. This indicates that NAFLD is common among men.

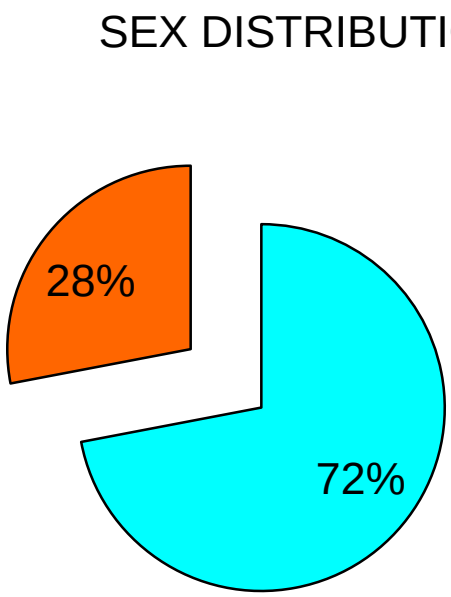


TABLE 3 : BMI DISTRIBUTION

BMI	NO OF CASES
<25	36
26-30	61
>30	3
Total	100

Among NAFLD patients 61% had BMI in the range of around 26 to 30.This indicates obesity plays major role in the pathogenesis of NAFLD.

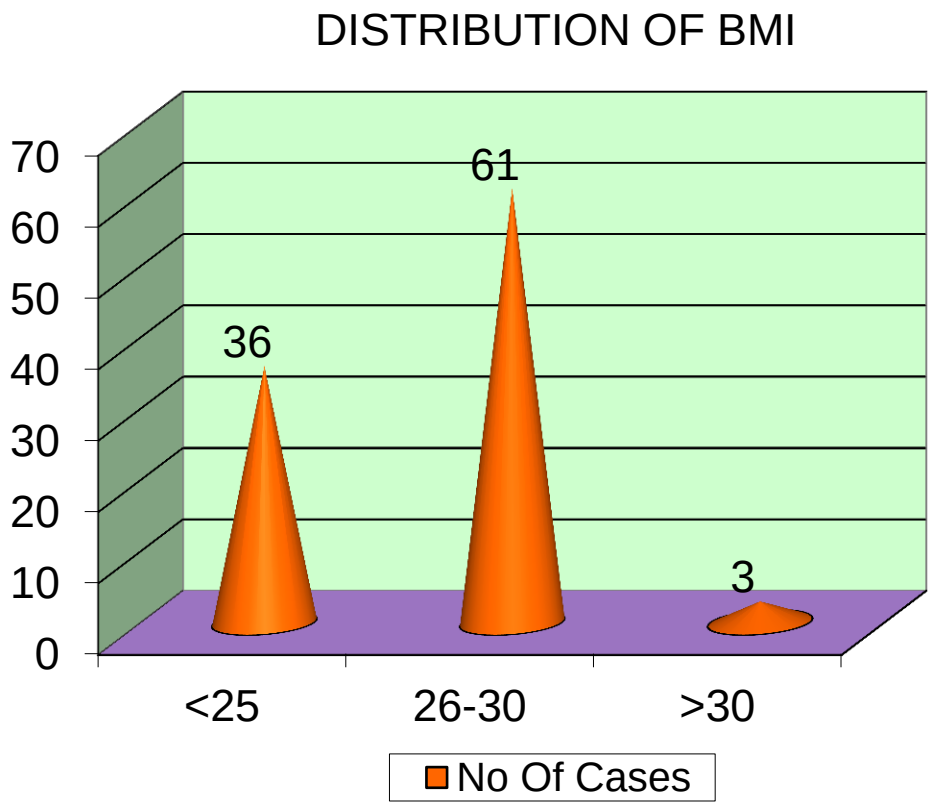


TABLE 4:WAIST CIRCUMFERENCE DISTRIBUTION

WAIST CIRCUMFERENCE	NO OF CASES
<75	18
76-90	50
>90	32
Total	100

Among NAFLD 50% had waist circumference in the range of around 76 to 90 cm.this indicates central obesity plays major role in pathology of NAFLD.

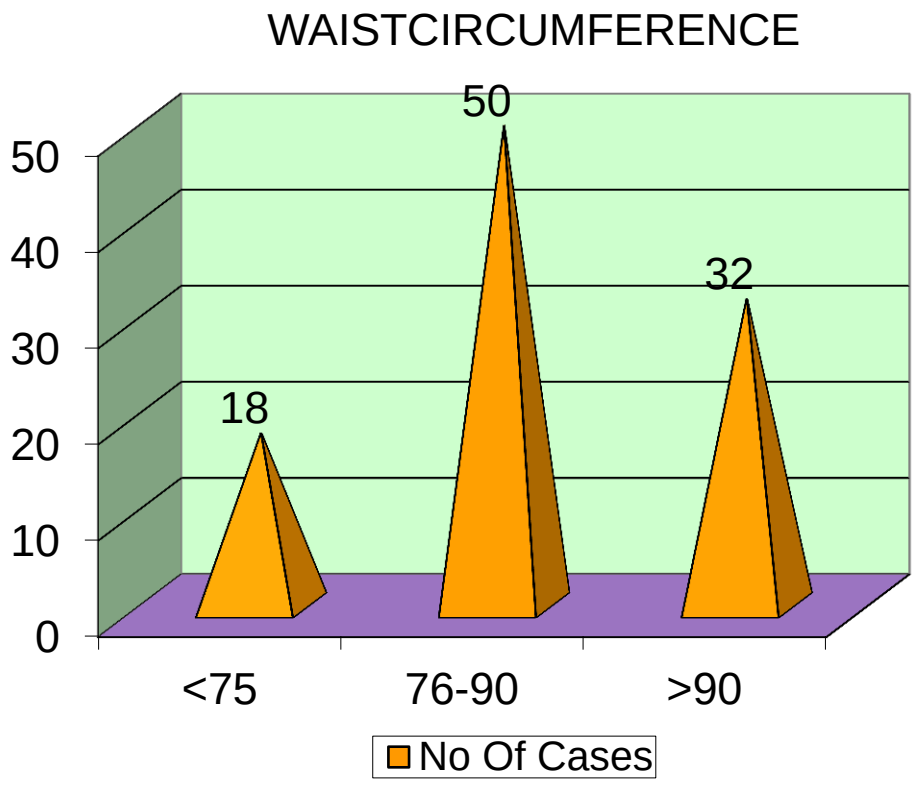


TABLE 5:FASTING BLOOD SUGAR DISTRIBUTION

FBS	NO OF CASES
<100	35
101-200	52
>200	13
Total	100

Among NAFLD patients 65% had fasting blood sugar >100mg/dl.This indicates diabetes mellitus plays role in the pathology of NAFLD.

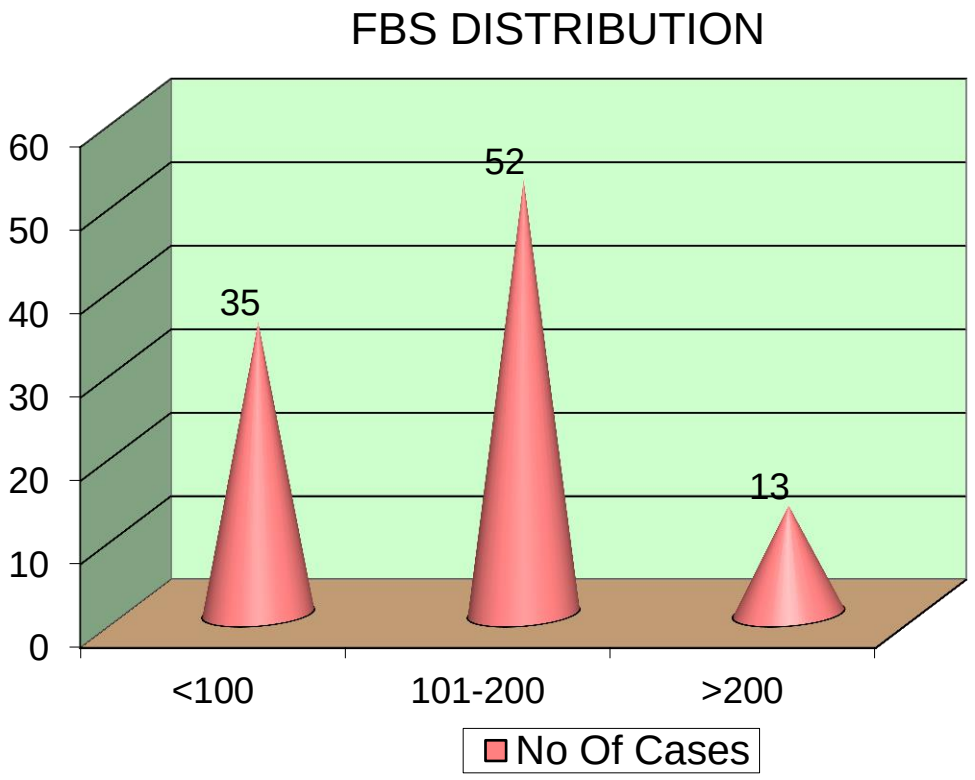


TABLE 6:BLOOD PRESSURE DISTRIBUTION:

SBP	No Of Cases
<130	23
131-150	58
>150	19
Total	100

Among NAFLD patients 77% had blood pressure >130 mm hg..This indicates hypertension is common association with NAFLD.

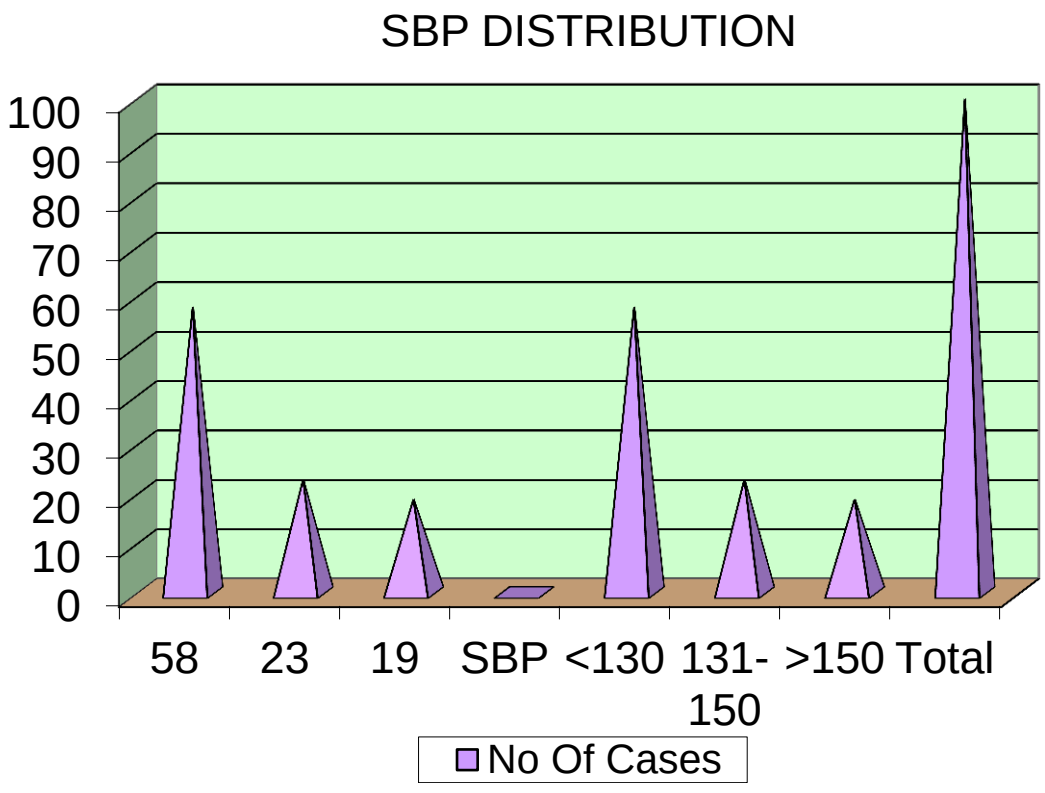


TABLE 7:DIASTOLIC BLOOD PRESSURE DISTRIBUTION:

DBP	No Of Cases
<85	59
86-100	35
>100	6
Total	100

Among NAFLD patients 41% patients have diastolic blood pressure above 85mm/Hg.

This indicates diastolic hypertension is also common in NAFLD.

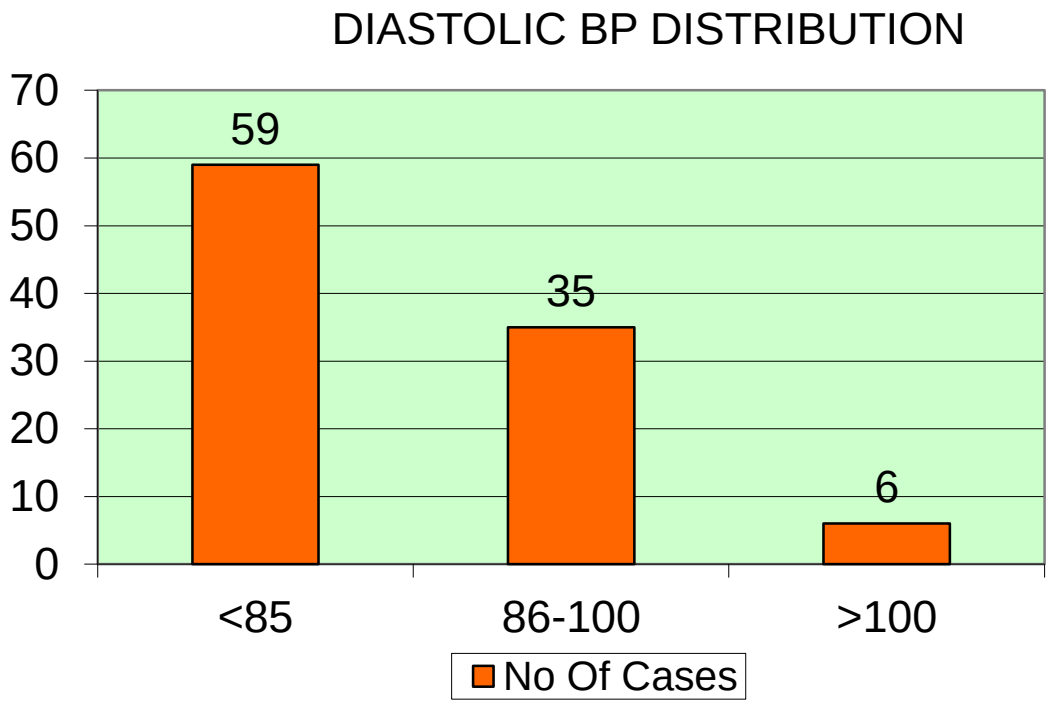


TABLE 8:ALANINE TRANSAMINASE DISTRIBUTION:

ALT	No Of Cases
<25	56
26-50	25
>50	19
Total	100

Among NAFLD patients 44% had increased enzyme activity. This indicates the NAFLD patients have chronic inflammation of the liver.

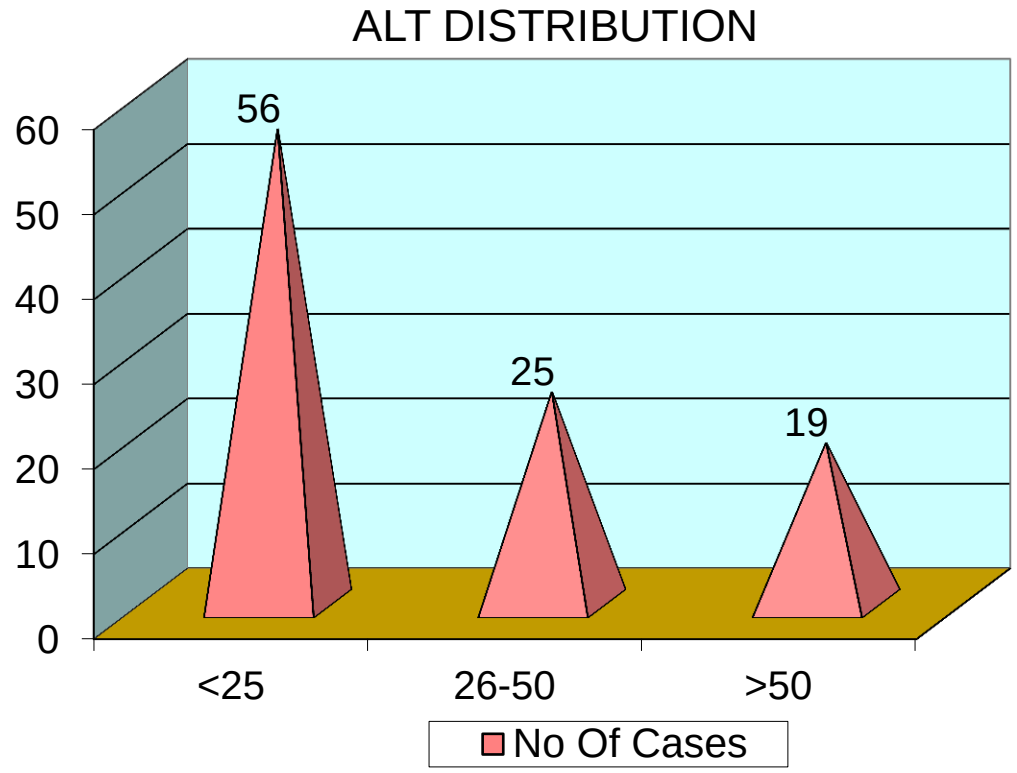


TABLE ALT AND MPV CORELATION:

ALT	Mean MPV	SD
<25 (56)	9.816	1.271
26-50 (25)	9.444	1.468
>50 (19)	10.232	0.87

In NAFLD patients whose ALT was high , MPV was also tend to be high. This shows the positive correlation between ALT and MPV. The mean MPV was 10.2 in elevated ALT patients.

TABLE : HDL AND TGL DISTRIBUTION

HDL	**No Of Cases**
<40	66
41-50	20
>50	14
Total	100

TABLE TGL DISTRIBUTION IN NAFLD PATIENTS

TGL	No Of Cases
<150	32
>150	68
Total	100

Among NAFLD patients 68 % of the patients had TGL >150 mg/dl and 66 % of patients have HDL cholesterol < 40 mg.dl.

TABLE 9:PLATELET DISTRIBUTION:

PLATELET COUNT	No Of Cases
<2.0	43
2.1-3.0	38
>3.0	19
Total	100

Among NAFLD patients 57% patients had elevated platelet count.This indicates platelet abnormality is common among NAFLD patients.

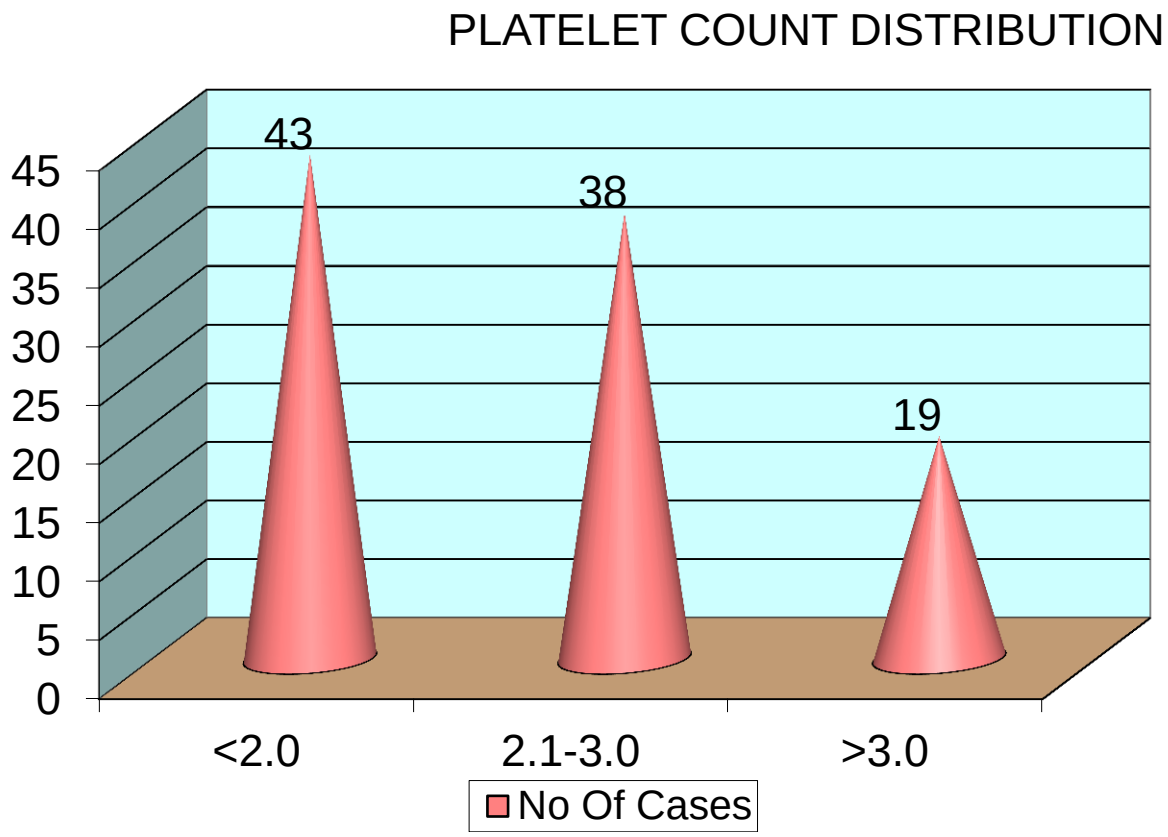


TABLE 10: MEAN PLATELET VOLUME DISTRIBUTION :

MPV	**No Of Cases**
<9.0	30
9.1-11.0	47
>11.0	23
Total	100

Mean platelet volume is increased in 70% patients in NAFLD. This indicates platelet volume and atherosclerosis is common among NAFLD patients.

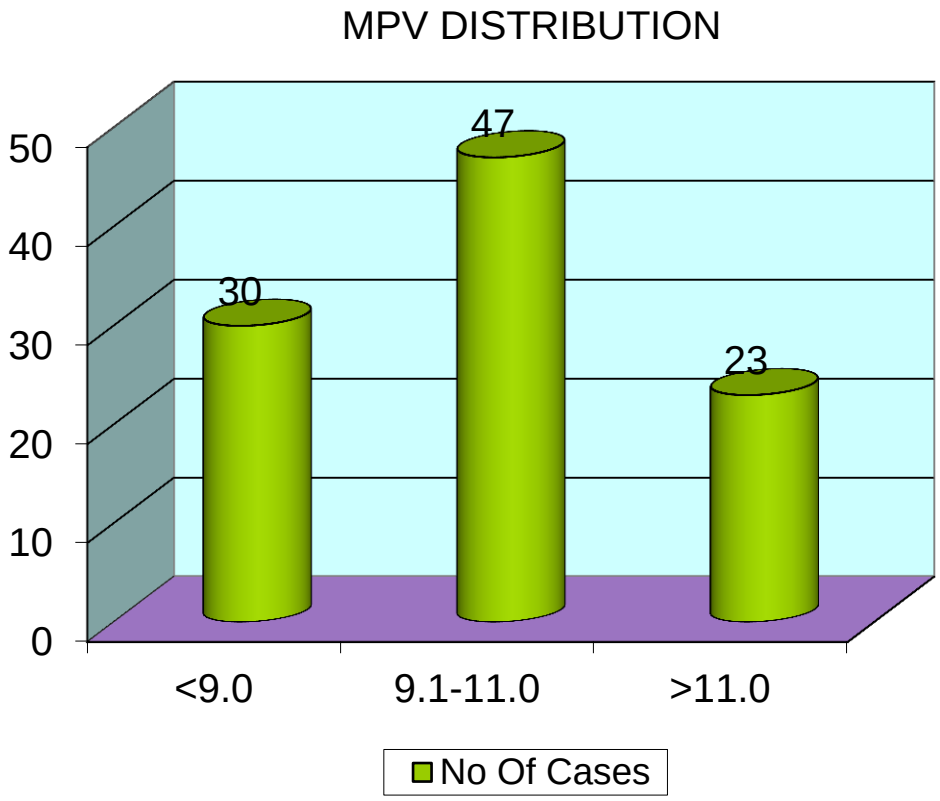


TABLE 11:ELECTRO CARDIOGRAPHIC CHANGES DISTRIBUTION:

ECG CHANGES	No Of Cases
P	53
A	47
Total	100

53% NAFLD patients had electrocardiographic changes. This indicates NAFLD is associated with cardiovascular disease. Also these ECG changes were associated with NAFLD patients with high MPV.

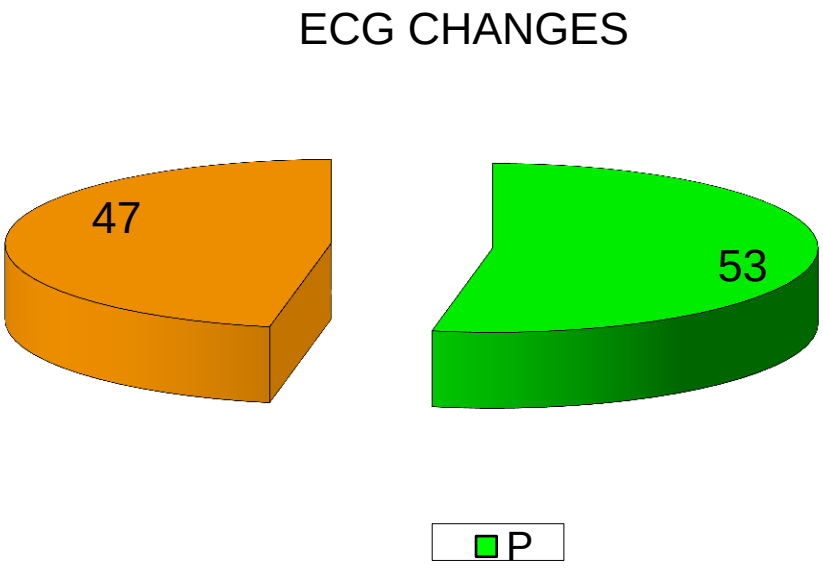


TABLE 12:BODY MASS INDEX VERSUS PLATELET COUNT DISTRIBUTION:

BMI VS PLATELET COUNT	Mean	SD	**P**
<25 (36)	2.186	0.779	0.356
26-30 (61)	2.292	0.771	
>30 (3)	1.667	0.764	

Among obese patients platelet counts were decreased .This indicates that obese individuals have platelet dysfunction and they are more prone to early atherosclerosis and cardiac morbitity.

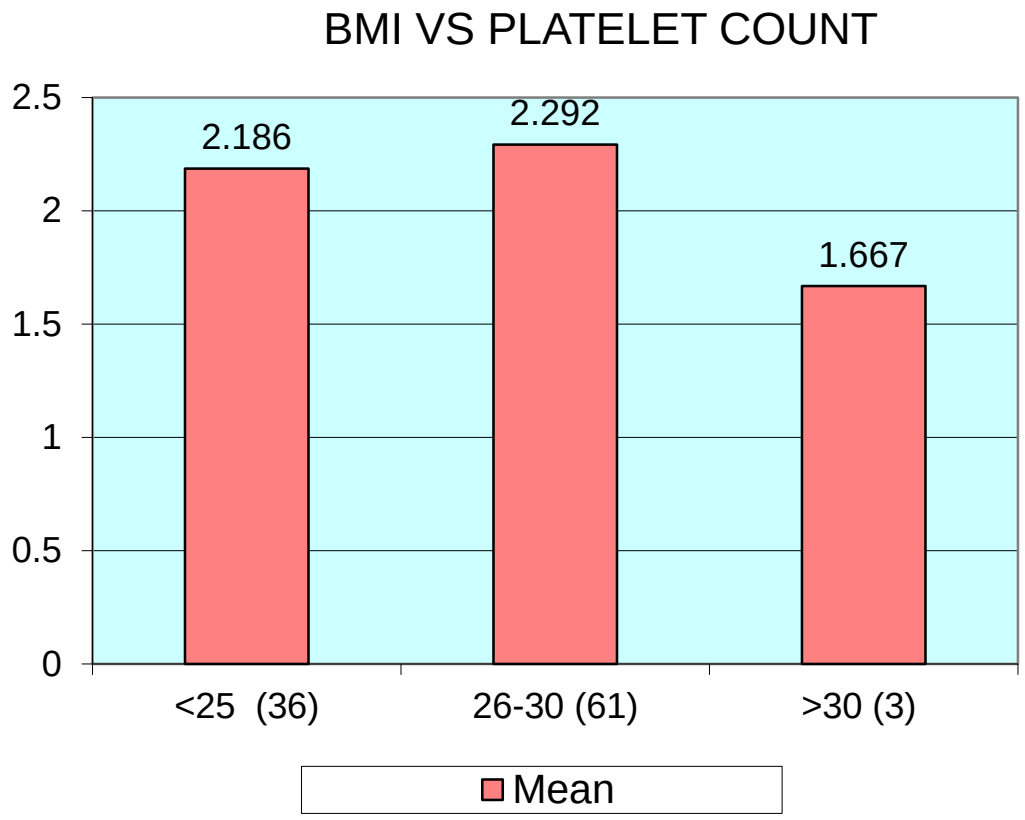
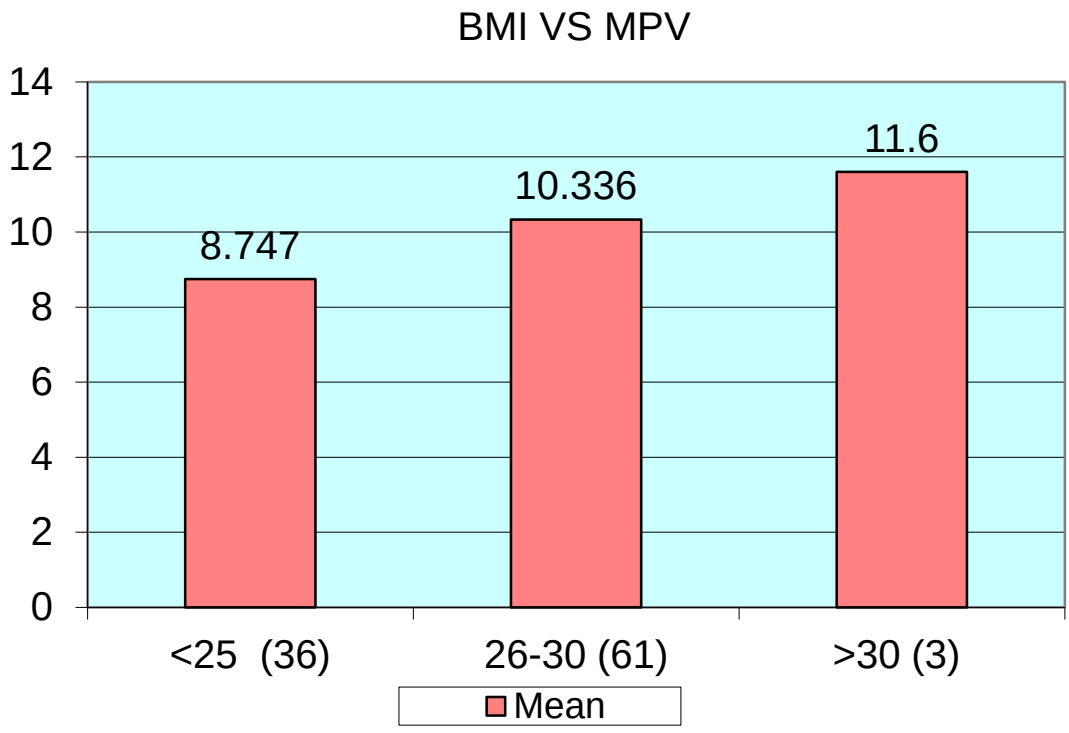


TABLE 13 : BMI AND MPV DISTRIBUTION

BMI VS MPV	Mean	SD	**P**
<25 (36)	8.747	0.935	<0.001
26-30 (61)	10.336	1.023	
>30 (3)	11.6	0.458	

Among obese patients MPV was increased. The mean MPV for BMI >30 was 11.6 which was significant .This indicates that obese individuals have platelet dysfunction and they are more prone to early atherosclerosis and cardiac morbitity.



DISCUSSION:

“This study was done in Government Rajaji Hospital which included 100 NAFLD patients who were selected randomly. All laboratory determinations were obtained after 12 fasting h. Enzymatic methods were used to measure fasting blood glucose, total and HDL-cholesterol, and triglyceride . ALT and AST levels were measured using the -ketoglutarate reaction; GGT levels with the L--glutamyl-3-carboxy-4-nitroaniliderate method.”

AGE AND SEX DISTRIBUTION :

“Among 100 patients , NAFLD are more common in age group of 40 to 50 years (56%). NAFLD is more common among males (72%) when compared to female (28%). Obesity and visceral adiposity were common in males and so NAFLD was common among males. Our findings are in agreement with the study Kopley et al, 2011 . However In a study **Mean platelet volume as a novel surrogate marker for early Non-Alcoholic Fatty Liver Disease** conducted by Walid Shehab-Eldin, Alaa Efat, Somaia Shehabeldeen, Abdallah Essa, Mohamed Shereef et al , there was no significant difference as regarding with age, sex.”

BMI DISTRIBUTION AND METABOLIC SYNDROME AND THEIR CORELATION WITH NAFLD

"In our study NAFLD is common among obese individuals with BMI 26 to 30 (61%). Among NAFLD patients 68 % of the patients had TGL >150 mg/dl and 66 % of patients have HDL cholesterol < 40 mg.dl. Among NAFLD 50% had waist circumference in the range of around 76 to 90 cm. This indicates central obesity plays major role in pathology of NAFLD. Among obese patients, platelet count was decreased and MPV was increased. The mean MPV was 11.6 for BMI>30. This indicates that obese individuals have platelet dysfunction and they are more prone to early atherosclerosis and cardiac morbidity."

" A previous study in Tehran had shown a strong correlation between NAFLD and BMI. The study "**Assessment of NAFLD cases and its correlation to BMI and metabolic syndrome in healthy blood donors in Kerman" conducted by** Sadroddin Lahsaee, Alireza Ghazizade et al found a correlation between NAFLD and metabolic syndrome and this is regarding that NAFLD is the hepatic component of metabolic syndrome."

"In other study "Non-Alcoholic Steatohepatitis (NASH): Risk Factors in Morbidly Obese Patients" conducted by Alexandre Losekann , Antonio C. Weston , Angelo A. de Mattos et all concluded that BMI does not always properly reflect the degree of visceral adiposity. The present results did not show a positive correlation of BMI with the degree of steatosis, NASH and fibrosis."

DIABETES MELLITUS AND NAFLD:

“Blood glucose was measured by enzymatic photometric test which aimed at determining blood glucose after enzymatic oxidation by glucose oxidase. The colorimetric indicator is quinoneimine, which is generated from 4-aminoantipyrine and phenol, under the catalytic action of peroxidase (Trender's reaction).”

“In the study , “ Lipid and Glucose Profile in Non-alcoholic Fatty Liver Disease: A Hospital Based Study”, sanaa M kamal, Fahad Abdullah Alghulaydhawi, Abdullah Omair Alsuayri, Mutlaq Mohammed Almutlaq, Rashed Ibrahim Alqunaian, Abdullah Sawma found that NAFLD was closely associated with obesity and diabetes mellitus. Diabetes and NAFLD often coexist, and there is evidence to suggest that diabetes can have a significant adverse effect on patients with NAFLD, leading to increased complications and premature mortality. The liver plays a unique role in controlling carbohydrate metabolism by maintaining glucose concentration in a normal range, expressing a number of enzymes that are alternatively turned on or off depending on whether blood glucose levels are either rising or falling.”

“In our study also diabetes mellitus was common in NAFLD individuals. Among NAFLD patients 65% had fasting blood sugar >100mg/dl. This indicates diabetes mellitus plays role in the pathology of NAFLD.”

“In a study “Correlation of Non-alcoholic Fatty Liver Disease and Diabetes Mellitus” conducted in Kanchipuram , Tamil nadu , it was statistically proven that there was strong co-relation as grading of fatty liver increases there is a marked increase in postprandial

sugar values. Thus which reveals that prevalence of diabetes mellitus is more when the severity of fat accumulation increases in the liver."

HYPERTENSION AND NAFLD:

"In our study, among NAFLD patients 77% had systolic blood pressure >130 mm Hg. This indicates hypertension is common association with NAFLD."

ALT AND NAFLD:

"In our study , among NAFLD patients 44% had increased enzyme activity. This indicates the NAFLD patients have chronic inflammation of the liver. Also in our study in NAFLD patients whose ALT was high , MPV was also tend to be high. This shows the positive correlation between ALT and MPV. The mean MPV was 10.2 in elevated ALT patients."

"In a study **"Assessment of NAFLD cases and its correlation to BMI and metabolic syndrome in healthy blood donors in Kerman**" , the prevalence of NAFLD among 35 subjects with persistently elevated serum ALT level was 63%. It seems that NAFLD is the most common cause of a persistently elevated ALT in blood donors from Kerman. In our study , among NAFLD patients 44% had increased enzyme activity. This indicates the NAFLD patients have chronic inflammation of the liver."

PLATELET COUNT AND MPV CORELATION WITH NAFLD:

“Mean platelet volume is increased in 70% patients in NAFLD. This indicates platelet volume and atherosclerosis is common among NAFLD patients.”

“Among obese patients MPV was increased. The mean MPV for BMI >30 was 11.6 which was significant .This indicates that obese individuals have platelet dysfunction and they are more prone to early atherosclerosis and cardiac morbidity. In the study , *“***Mean platelet volume in patients with non-alcoholic fatty liver disease”** by Ozhan H, Aydin M et al states that NAFLD patients had significantly higher body mass index compared to the control cases. Among biochemical variables, fasting plasma glucose and triglyceride were significantly higher in the NAFLD group. NAFLD cases also had lower platelet count and higher MPV . MPV was positively correlated with AST , ALT level and the presence of NAFLD but negatively correlated with platelet number and creatinine. In another study “Mean platelet volume in biopsy-proven non-alcoholic fatty liver disease” by Celikbilek M et al showed that MPV, an indicator of platelet activation, increased in biopsy proven NAFLD patients.”

MEAN PLATELET VOLUME AS A MARKER FOR CV RISK IN NAFLD:

“In our study , 53% NAFLD patients had electrocardiographic changes. This indicates NAFLD is associated with cardiovascular disease. Also these ECG changes were associated with NAFLD patients with high MPV(11.6 fL). In this study conducted by

Naim Alkhouri, Gaurav Kistangari et al, " **Mean Platelet Volume as a Marker of Increased Cardiovascular Risk in Patients with Nonalcoholic Steatohepatitis**" ,there was a stepwise significant increase in MPV levels from patients with normal biopsies to patients with simple steatosis to patients with NASH (9.5 fL, 10.2 fL, and 11.3 fL, respectively). Moreover, there was a significant correlation between MPV levels and the individual histological features of NASH on liver biopsy including inflammation, steatosis , ballooning and fibrosis ."

CONCLUSION:

“1.Among 100 patients , NAFLD are more common in age group of 40 to 50 years (56%). NAFLD is more common among males (72%) when compared to female (28%).”

“2. NAFLD is common among obese individuals with BMI 26 to 30 (61%). Among NAFLD patients 68 % of the patients had TGL >150 mg/dl and 66 % of patients have HDL cholesterol < 40 mg.dl. Among NAFLD 50% had waist circumference in the range of around 76 to 90 cm.”

“3. In our study also diabetes mellitus was common in NAFLD individuals. Among NAFLD patients 65% had fasting blood sugar >100mg/dl. This indicates diabetes mellitus plays role in the pathology of NAFLD.”

“4. In our study , among NAFLD patients 44% had increased enzyme activity. This indicates the NAFLD patients have chronic inflammation of the liver. Also in our study in NAFLD patients whose ALT was high , MPV was also tend to be high. This shows the positive correlation between ALT and MPV. The mean MPV was 10.2 in elevated ALT patients.”

“5. Mean platelet volume is increased in 70% patients in NAFLD. This indicates platelet volume and atherosclerosis is common among NAFLD patients.

Obese patients had increased MPV . The mean MPV for BMI >30 was 11.6 which was significant .This indicates that obese individuals have platelet dysfunction and they are more prone to early atherosclerosis and cardiac morbidity.”

“6. In our study , 53% NAFLD patients had electrocardiographic changes. This indicates NAFLD is associated with cardiovascular disease. Also these ECG changes were associated with NAFLD patients with high MPV(11.6 fL). This association shows that MPV can be used to asses cardiovascular risk in NAFLD patients.”

SUMMARY:

“The study “ MEAN PLATELET VOLUME AS A NOVEL MARKER FOR INCREASED CARDIOVASCULAR RISK IN PATIENTS WITH NON ALCOHOLIC FATTY LIVER DISEASE” was done to assess whether MPV is increased in NAFLD patients and to investigate whether this increased MPV is associated with increased cardiovascular disease in patients with NAFLD .”

“100 patients were selected carefully and were evaluated on clinical , social and laboratory aspects after institutional ethical clearance . NAFLD patients were selected on the basis of Ultrasonographic findings and blood tests were carried out to determine MPV. ECG was taken to all patients and was sorted into two groups as patients with ECG changes and patients without . Those patients with ECG changes had mean MPV value increased and thus MPV can be used as novel marker to assess cardiovascular risk. Also MPV showed a positive correlation with ALT which also indicates that MPV is an inflammatory marker. This study also demonstrates significant correlation between MPV and metabolic syndrome.”

“Although MPV is a cheap and simple test, it is usually neglected by clinicians. Its importance in patients with NAFLD is not only in the prediction of the disease but also in the prediction of cardiovascular mortality in patients with already diagnosed NAFLD. Our data explain in part the increased cardiovascular mortality in patients with NAFLD”

LIMITATIONS OF THE STUDY:

“1.The small sample size and the cross-sectional design impose the data obtained to be confirmed in wider trials.”

“2.The diagnosis of NAFLD was performed by using the non-invasive Ultrasonographic guidance instead of liver biopsy that represents the gold standard.”

“3.For assessing cardiovascular risk among NAFLD patients , only ECG was taken.”

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LIST OF ABBREVIATIONS:

NAFLD : Non alcoholic fatty liver disease .

MPV : Mean platelet volume.

METS: Metabolic syndrome.

NASH: Non alcoholic steatohepatitis.

NAFL: Non alcoholic fatty liver.

UPR: Unfolded protein response.

PERK : Protein kinase RNA like ER kinase.

IRE 1 α: Inositol requiring protein.

ATF 6 : Activating transcription factor.

SREBP: Sterol responsive element binding protein.

ROS : Reactive oxygen species.

SFA: Saturated fatty acid

KC: Kupfer cells.

HSC: Hepatic stellate cells

SOCS: Supressor of cytokine signalling.

CCL2: C Chemokine ligand 2.

AMPK: AMP activated protein kinase.

PROFORMA

Name:

Age / Sex:

IP / OP no:

Occupation:

Presenting complaints:

H/o right upper abdominal pain

H/o heaviness over right upper abdomen

H/o easy fatigue

H/o nausea & anorexia

H/o generalised weakness

H/o itching

Past History:

H/o DM/SHT/CKD/CLD/VIRAL HEPATITIS/THYROID DISEASE

H/O Blood transfusion/HIV/tattoing/hepatotoxic drugs/oc pills

Personal history

alcoholic/ non alcoholic

smoker/ nonsmoker

Clinical Examination:

GENERAL EXAMINATION

Conscious

Pallor

Icterus

Clubbing

Goitre

Lymphadenopathy/signs of liver cell failure.

Scratch marks/tattoo marks

VITALS

Pulse rate

Blood pressure

Height

Weight

BMI

Waist : hip ratio

SYSTEM EXAMINATION

Oral cavity

Abdomen

CVS

RS

CNS

Laboratory investigations:

1.Hemoglobin,complete blood count, Mean platelet volume

2.Blood urea, serum creatinine, blood glucose(FBS,PPBS)

3.Liver function tests including serum bilirubin,transaminases.

4.Viral markers

5.Fasting lipid profile.

6.USG ABDOMEN

7.ECG

Diagnosis

MASTER CHART

S.N	AGE	SEX	BMI	W.C	FBS	SBP	DBP	ALT	AST	T.C	LDL	HDL	TGL	PLT. C.	MPV	ECG
1	43	M	25.5	90	110	140	90	54	51	225	120	45	156	1.5	10.1	P
2	45	M	22.3	87	100	130	85	15	14	145	89	46	145	1.5	9.8	A
3	42	M	21.4	78	98	120	80	55	48	222	135	48	112	3.1	8.7	A
4	50	M	26	91	118	135	70	10	18	155	118	39	152	2.3	9.5	A
5	49	M	25.7	90	123	140	95	50	55	232	138	40	212	3.2	10.2	P
6	62	M	25.3	89	121	120	90	20	15	158	122	41	209	1.4	10.2	P
7	29	M	22.4	76	87	165	95	25	20	177	78	39	167	2.2	9.2	A
8	24	F	25.6	82	130	140	85	15	19	198	98	45	121	3.3	10.2	P
9	30	M	29.4	98	145	130	100	55	45	255	120	38	244	2.9	11.2	P
10	43	F	26.3	90	134	120	90	10	18	166	156	43	134	2.3	11.1	P
11	41	M	21.6	78	100	110	80	25	22	176	87	44	154	2.8	9.3	A
12	52	M	27.3	96	187	155	75	22	30	178	156	47	231	2.5	10.2	P
13	56	M	26.5	93	167	120	70	20	28	155	123	56	157	1	9	A
14	50	F	24.9	87	101	110	75	15	24	146	87	53	214	2.2	11.2	P
15	42	M	21.9	76	95	170	95	10	19	155	97	58	112	1.2	8	A
16	62	M	26	89	109	130	80	44	45	232	110	43	145	3.5	8.2	A
17	32	F	22	62	92	140	85	15	19	177	76	46	113	2.8	7.9	A
18	47	M	21.7	75	93	110	80	28	20	156	88	32	121	1.4	7.6	A
19	42	M	24.9	78	80	165	75	39	40	227	115	48	154	3.4	7.9	A
20	38	F	32	104	212	120	100	46	38	265	127	33	265	2.5	11.1	P
21	44	M	23.6	88	100	160	80	29	20	147	98	46	154	1	8.5	A
22	47	M	30	102	231	130	85	18	10	150	195	34	254	1.4	11.9	P
23	43	M	28.5	99	211	110	75	17	24	167	178	36	232	2.8	10.2	P
24	44	F	24.3	70	83	150	105	50	46	245	130	48	154	1.6	7.5	A
25	39	M	29.3	100	209	170	75	23	29	177	197	38	199	1.5	10.9	P
26	42	M	25.3	87	111	140	80	30	20	177	115	43	143	2.2	8.9	A
27	50	F	22.5	76	92	110	85	17	20	155	116	46	154	1	7.2	A
28	58	M	27.8	97	165	145	90	55	50	243	119	32	234	1.4	11.1	P
29	39	M	29.9	101	187	110	95	18	20	150	199	34	265	3.1	11.6	P
30	41	M	25.1	88	125	120	85	18	20	148	88	47	223	1.1	8.5	A
31	66	M	22	78	92	120	110	20	15	155	99	46	132	1	8.3	A
32	54	F	22.6	63	93	110	70	43	45	222	110	47	102	3.4	8.6	A
33	44	F	22.4	78	100	120	75	25	30	155	86	45	108	1.6	8.3	A
34	39	M	29	99	190	130	70	20	25	160	117	34	232	1.8	11.8	P
35	50	M	30	102	211	110	100	37	35	234	115	37	276	2.4	11.5	P
36	43	F	21.5	70	89	120	70	45	40	254	118	46	114	1.6	7.8	A

37	45	M	27.2	98	178	110	75	44	54	222	110	36	212	1.5	11.1	P
38	61	M	20	73	98	140	70	40	52	227	112	62	123	2.1	7.9	A
39	49	F	28.2	84	190	110	95	18	25	160	187	37	198	1.2	11	P
40	42	M	25.4	75	118	110	80	25	19	165	116	45	156	1.2	8.9	A
41	60	F	25.3	81	112	120	75	65	68	255	110	54	158	2.7	10.2	P
42	38	F	26.6	80	167	120	70	55	45	245	126	36	159	1.8	9.4	P
43	46	M	25.6	76	145	110	75	30	33	180	112	36	132	1.9	9.2	A
44	48	M	25.3	80	187	135	90	67	65	233	109	43	134	2.7	9.4	A
45	37	F	19.9	57	98	110	85	40	45	210	80	45	113	3.1	8.3	A
46	57	M	28.4	90	187	120	90	15	20	165	145	38	187	2.4	11.3	P
47	45	M	26.4	88	197	110	70	78	75	265	134	32	156	2.2	11.2	P
48	55	M	26.7	83	194	120	90	16	20	165	167	36	154	1.3	9.7	P
49	51	F	25.7	80	192	155	95	20	29	156	124	41	198	3.2	10.2	P
50	49	F	21	71	91	130	90	25	23	145	89	40	114	3.3	7	A
51	50	M	26.5	87	185	155	100	72	65	255	113	52	165	3	10.2	P
52	53	M	28.9	91	298	165	110	12	16	176	145	37	190	2.1	11.8	P
53	65	M	24	76	93	135	90	18	29	167	65	45	123	1.5	9.5	A
54	53	M	23	72	90	135	100	45	48	222	112	43	111	2.8	8.4	A
55	55	M	22.6	72	99	155	85	70	73	227	98	42	106	2.5	9.4	A
56	42	M	26.8	82	155	110	70	25	29	154	134	37	145	3.2	10.2	P
57	60	F	21	74	93	165	75	35	30	177	89	34	102	1.2	8.6	A
58	50	M	25.9	88	165	120	95	30	23	156	132	37	112	1.8	8.5	A
59	51	M	25.6	90	164	110	85	16	12	165	154	39	155	1.3	9.3	A
60	55	M	26.1	91	132	135	70	82	74	276	132	36	165	2.5	10.2	P
61	41	F	24	73	92	140	75	18	10	155	113	45	132	2	9.3	A
62	65	M	27.3	99	167	135	80	16	35	165	167	37	231	2.1	10.9	P
63	53	F	29.6	87	234	110	80	13	20	155	156	40	242	3.1	11.1	P
64	49	M	22.4	78	95	145	75	22	37	154	97	43	132	2.5	10.1	P
65	39	F	25.6	88	176	130	90	84	66	245	87	40	165	2.7	8.9	A
66	37	F	28.5	90	198	120	100	55	54	190	90	33	212	3.7	10.2	P
67	43	M	26.2	91	134	110	75	18	22	162	113	56	165	2.6	10.2	P
68	41	M	30	101	276	120	95	22	10	153	176	33	287	1.7	11.5	P
69	63	M	26.5	99	143	150	85	50	55	210	113	65	232	2.1	11	P
70	46	M	20.5	75	91	110	80	18	22	176	112	34	113	2.7	10.2	P
71	39	F	31.9	102	298	120	105	14	19	154	156	33	267	1.5	12	P
72	55	M	21.4	72	90	130	100	76	70	265	98	46	112	3	9.5	A
73	49	M	30	103	243	155	90	28	20	154	176	35	254	2.5	11.5	P
74	56	F	22.5	76	88	110	85	15	38	155	98	46	103	2.9	9.2	A
75	52	M	30.3	101	232	110	105	22	10	165	154	35	254	1	11.7	P
76	64	M	21.6	70	70	125	70	25	18	176	110	57	102	2.9	9.3	A
77	66	M	27.4	99	154	150	80	66	58	245	189	43	265	1.7	12	P

78	53	M	26.8	95	123	120	75	18	25	167	94	35	154	1.9	11.2	P
79	55	M	29.9	102	169	130	70	45	39	200	143	31	287	4.2	12	P
80	51	M	20.7	80	74	110	110	13	10	154	87	45	90	1.8	9.2	A
81	56	M	26.8	90	156	155	75	43	39	221	116	42	156	1.9	9.6	A
82	64	M	28.5	92	165	120	70	65	55	234	167	34	212	3.1	10.9	P
83	57	F	20.9	76	77	130	80	10	15	155	89	57	95	2.9	9.2	A
84	52	M	26.4	92	143	110	85	45	49	230	184	43	210	3.3	11	P
85	49	M	25.7	91	176	160	100	12	10	154	87	56	102	1.4	10.3	P
86	65	M	25.3	90	156	140	75	20	10	165	113	56	211	1.3	8.9	A
87	53	M	27.8	94	198	135	80	62	55	255	145	54	190	3	11	P
88	67	F	30	104	267	160	90	45	38	222	178	35	199	2.4	11.3	P
89	54	M	22.8	78	76	135	85	25	20	160	98	32	115	2.8	10.2	P
90	56	M	26.7	80	156	110	80	10	15	167	114	41	121	3.3	10.3	P
91	50	M	20.5	70	87	135	95	12	10	153	89	43	99	1.7	9.3	A
92	56	M	26.8	90	145	170	85	55	30	255	115	35	143	1.6	10.5	P
93	45	M	25.6	89	143	130	80	20	22	154	134	56	114	3.1	8.4	A
94	53	M	20.6	79	89	120	90	15	10	161	92	42	115	2.7	8.3	A
95	56	F	23.7	65	92	165	95	10	15	172	93	32	105	1.4	8	A
96	51	M	21.6	76	76	110	100	25	20	156	97	45	90	1.1	8.2	A
97	43	M	26.8	98	176	120	95	44	40	211	115	45	113	1.4	9.9	P
98	55	M	25.3	91	156	160	85	20	15	154	119	33	87	3.2	8.4	A
99	41	F	27.8	82	212	140	90	56	43	245	189	37	156	2.9	10.3	P
100	42	F	28.9	82	190	165	90	20	19	177	127	37	189	2	11.1	P

BMI : Body mass index

W.C : Waist circumference.

FBS: Fasting blood sugar.

SBP: Systolic blood pressure.

DBP: Diastolic blood pressure.

T.C: Total cholesterol.

LDL: Low density lipoprotein

HDL: High density lipoprotein.

TGL: Triglycerides

PLT.C : Platelet count

MPV : Mean platelet volume

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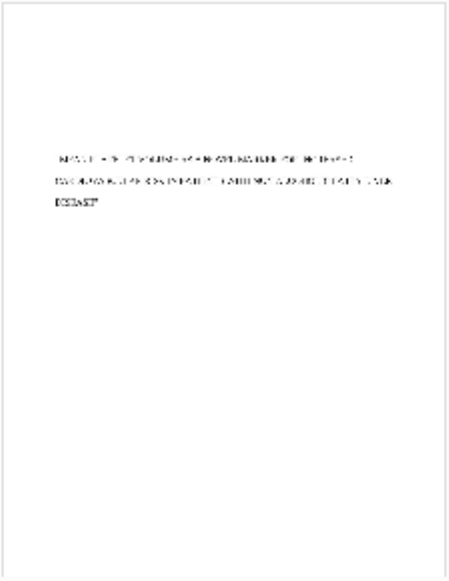

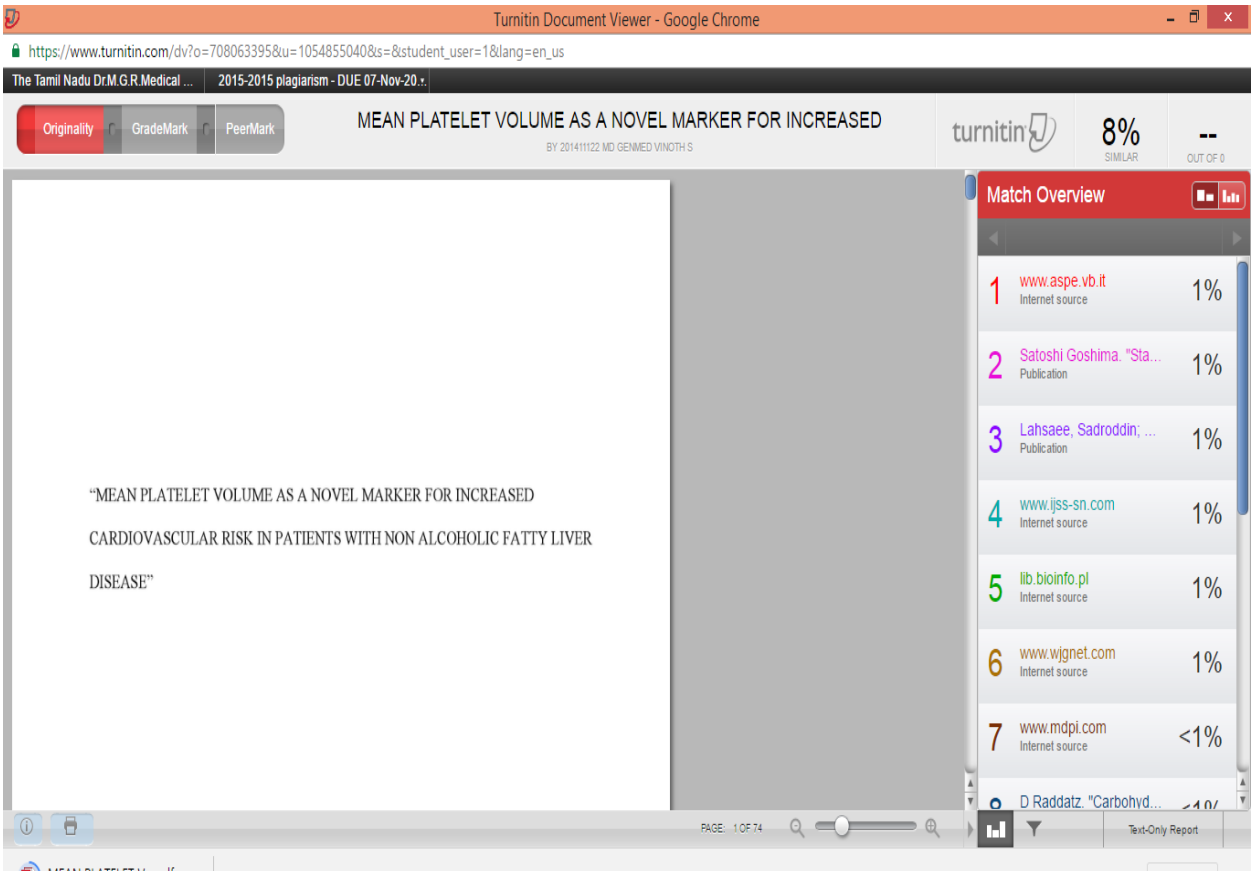
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Name of the Candidate	:	Dr.ABITHA ALIYAR
Course	:	PG in MD GENERAL MEDICINE
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A STUDY ON NON-INVASIVE PREDICTORS OF LARGE OESOPHAGEAL VARICES IN PATIENTS WITH CIRRHOSIS
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